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A CORRELATIVE HISTOPATHOLOGIC STUDY OF EXPERIMENTAL SURGICAL REFLUX ESOPHAGITIS

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THE PREVALENCE of the problem of reflux esophagitis has only recently been emphasized. A lack of adequate correlation of gross and microscopic studies is evident from a survey of the literature. Therefore, a controlled histopathologic study of the course of the disease is presented in order to help clarify the clinical picture and provide concrete means to evaluate surgery involving the gastroesophageal junction.

In the past 25 years, the improvements in technique for examination of the esophagus have accentuated the importance of this organ as a site of inflammation. Endoscopy has provided a method of direct observation in the living subject. In addition, a current interest associated with the development of esophagitis after gastroesophageal surgery necessitates a detailed knowledge of the significant pathologic changes encountered. To date, endoscopic, roentgenologic, gross, and microscopic examinations of the esophagus have resulted in a confusion of terminology. The terms mild, moderate, erosive, ulcerative, peptic, subacute, granulomatous, streaking, patchy, erythematous, and edematous have been used. These terms, for the most part, have not been correlated with microscopic pictures. The net result is that, although the presence of the disease can be detected, its course and severity have been confused. The terminology mentioned reveals the inadequate appreciation of the dynamic pathologic process involved in this disease.

Giuseffi attempted an endoscopic (macroscopic) classification which is as follows: (1) Mild esophagitis indicated hyperemic edema and congestion with an intact mucosal layer. (2) Moderate esophagitis was localized intense inflammation with mucosal erosion or epithelial desquamation. (3) Severe esophagitis implied frank ulceration with oval ulcers containing a central yellowish gray slough, surrounded by hyperemia and usually situated in the longitudinal folds.

Kiriluk and Merendino used a controlled drip of one-tenth normal hydrochloric acid and 1 per cent pepsin for a period of from 15 minutes to 15 hours and observed acute changes in the esophagi in dogs. All esophagi exhibited erosions and ulcers at periods

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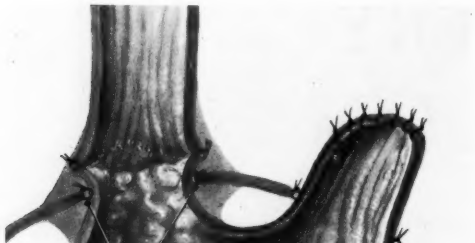

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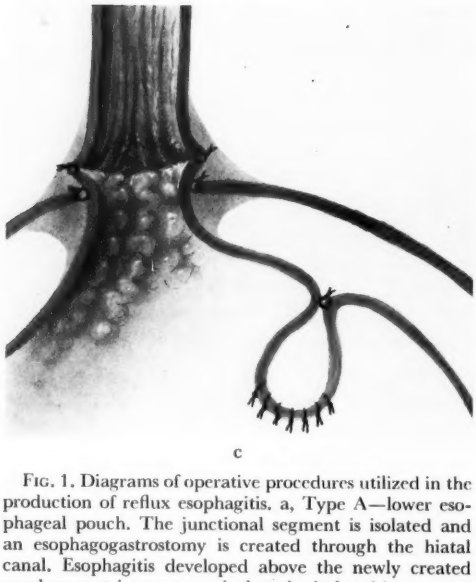

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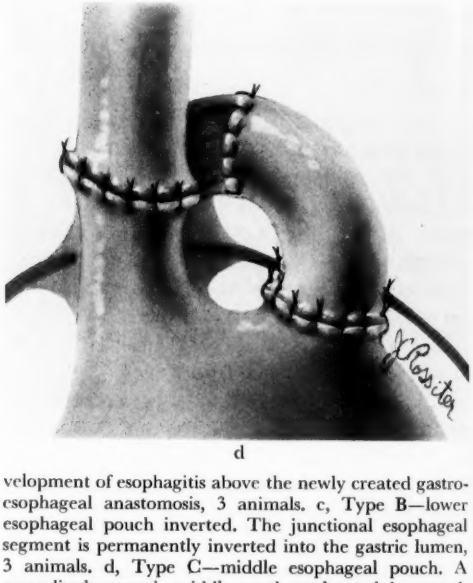

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FIG. 1. Diagrams of operative procedures utilized in the production of reflux esophagitis. a, Type A—lower esophageal pouch. The junctional segment is isolated and an esophagogastrostomy is created through the hiatal canal. Esophagitis developed above the newly created esophagogastric anastomosis, but the isolated innervated pouch remained intact, 19 animals. b, Type D—original continuity re-established. The intact isolated junctional segment is returned to its anatomic position after the development of esophagitis above the newly created gastroesophageal anastomosis, 3 animals. c, Type B—lower esophageal pouch inverted. The junctional esophageal segment is permanently inverted into the gastric lumen, 3 animals. d, Type C—middle esophageal pouch. A supradiaphragmatic middle esophageal pouch is created, 4 animals. Esophagitis inevitably developed in these pouches in contrast to junctional pouches in which esophagitis never developed when put in comparable position.

varying from 1 to 15 days. Redo and Barnes found that gastric secretions were responsible for esophageal inflammation. However, in none of these studies was a situation created which corresponded to that which occurs in humans when esophagogastric competence has been lost. Therefore, it was believed that a detailed study of the development of esophagitis in dogs after loss of esophagogastric competence would simulate clinical postoperative esophagitis and further elucidate the process. This knowledge could then be used to evaluate the efficacy of various procedures utilized to reconstruct

the esophagogastric junction. From material obtained during the initial investigation (2) together with supplementary procedures, this study was made.

METHOD

Twenty-nine animals were subjected to 4 separate types of operative procedures (Fig. 1), and studies were carried out for a period of from 1 week to 20 months. In our initial study in which the vestibular segment was isolated as a supradiaphragmatic pouch and a gastroesophageal anastomosis performed through the hiatal canal, type A, esophagitis developed inevitably above the newly created gastroesophageal anastomosis. Observations made through the esophagoscope and at autopsy indicated that the time of appearance and the severity of development of esophagitis varied even though it always occurred. It was also noted that with the return of the intact supradiaphragmatic pouch to its original position, type D, a reversal of the esophagitis could be effected. In addition, vestibular pouches inverted permanently into the gastric lumen, type B, rapidly developed a severe esophagitis. Finally, the midportion of the esophagus when isolated as a supradiaphragmatic pouch, type C, and thus exposed to gastric reflux, invariably developed inflammatory changes.

Material from this study was thus readily available for microscopic analysis in comparison with gross observations. The specimens were sectioned at multiple sites for histologic study. Two to 3 longitudinal sections were cut at the gastroesophageal anastomosis and 3 to 4 transverse sections were obtained from the esophagus at higher levels, depending upon the extent of the lesion. Microscopic observations included study of the separate layers of the esophageal wall.

In order to evaluate (1) the factor of silk suture granuloma—initially No. 4-0 silk sutures were used for all anastomoses—and (2) the initial stages of esophagitis, an additional group of animals was operated upon by the same technique but with catgut sutures for the anastomosis. These animals were sacrificed at specified intervals of from 1 to 6 weeks. Initial studies indicated that esophagitis usually developed in this period of time after operation. Specimens were studied by serial sections if the nature and extent of the disease process were questionable. All microscopic sections were stained with hematoxylin and eosin.

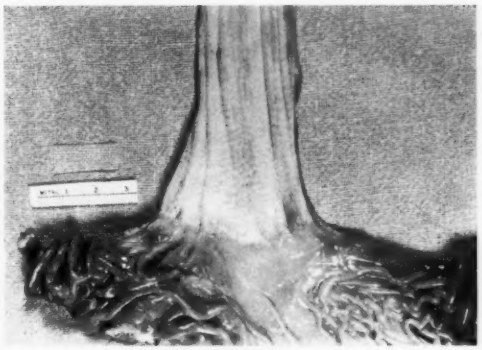

FIG. 2.

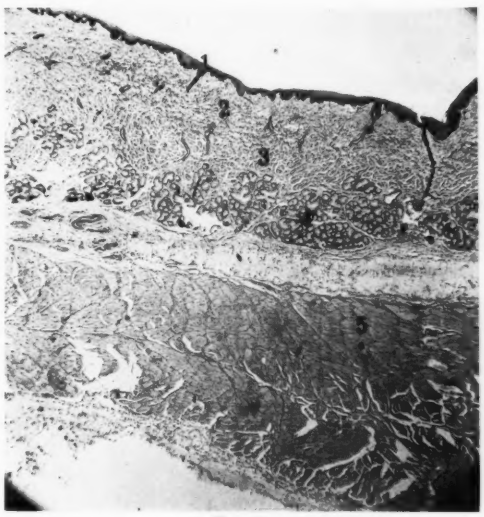

FIG. 3.

FIG. 2. Normal esophageal mucosa is illustrated. Note longitudinal folds and white glistening epithelial surface.

FIG. 3. Photomicrograph of normal lower esophageal wall: epithelium (*1*), lamina propria (*2*), muscularis mucosa (*3*), mucous glands (*4*), and muscularis externa (*5*). The epithelium and lamina propria comprise the mucosa; and the muscularis mucosa and mucous glands, the submucosa.

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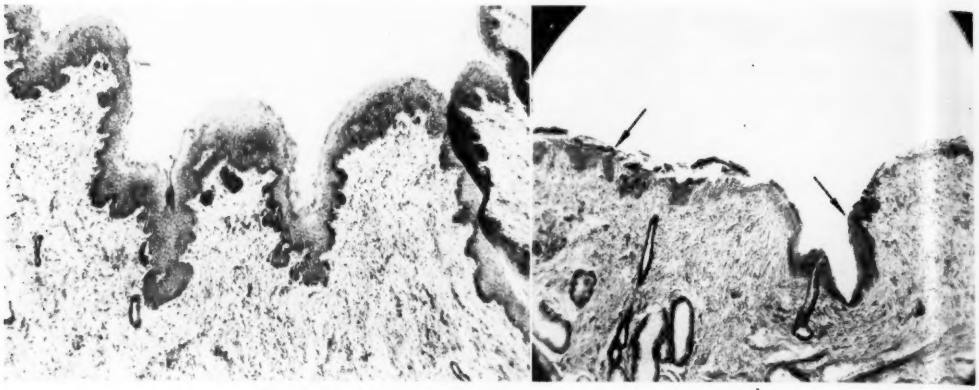

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FIG. 4.

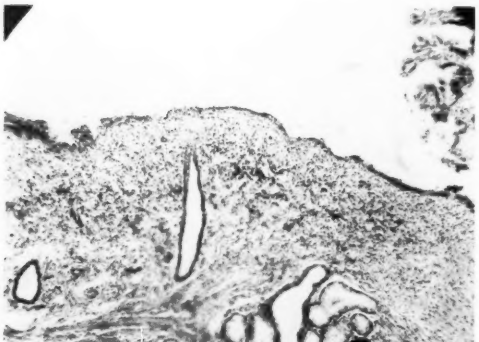

FIG. 5.

FIG. 4. a, Section from the lower one-third of the esophagus shows early stage 1 change in 3½ weeks. Note necrosis of the superficial layers of the epithelium while the basal layers remain intact. ×53. b, Section from the lower one-third of the esophagus of dog sacrificed 4 weeks after operation. Late stage 1 change is apparent. Arrow at left points to area of total epithelial necrosis. Compare with area of normal epithelium indicated by arrow on the right. ×43.

FIG. 5. Stage 2 changes are illustrated in a different area of the lower esophagus of same dog as shown in Figure 4b. There is loss of epithelium and a structurally intact lamina propria throughout with scattered acute inflammatory cell infiltration. ×17.

RESULTS

Figures 2 and 3 represent the normal gross and microscopic appearance of the lower esophagus. After careful analyses of the microscopic sections and comparison of each with its gross counterpart, the study indicated that the disease process went through the following stages of development:

Stage 1. Grossly, the mucosa displays a white, glistening surface and uniform vertical folds which is the normal appearance of esophageal mucosa in the dog (Fig. 2). Microscopically, there is necrosis of the epithelium with loss of nuclei which at first involves the superficial layers and later the entire thickness of the epithelium (Fig. 4a and b).

Stage 2. Grossly, the appearance is normal (Fig. 2). Microscopically, the epithelial layer has desquamated in patchy areas, and in the areas with epithelial loss, the lamina propria and, occasionally, the submucosa show a scattered infiltration of inflammatory cells with a predominance of polymorphonuclear leucocytes, occasional lymphocytes, plasma cells, and eosinophils. Edema may be present. The lamina propria retains its normal architecture, and there may be evidence of epithelial regeneration (Fig. 5).

Stage 3. Grossly, there is discreet oval or triangular ulceration of varying depth with smooth or punched-out margins or pink, purplish, red edematous areas localized or streaked, usually involving the lower 3 to 4

a b

FIG. 6.

FIG. 6. a, An acute ulcer crater is shown with a straight margin on the stomach side and a terraced margin on the esophageal side. There is destruction of epithelium, lamina propria, muscularis mucosa, mucous glands, and muscularis externa. A massive infiltrate of polymorphs and fibrin comprise the base of the ulcer, stage 3. ×15. b, Higher magnification of Figure 6a shows the heavy infiltration of the base of the ulcer with acute inflammatory cells, stage 3. ×110.

FIG. 7. Gross specimen taken from dog sacrificed at 3½ weeks shows the "punched-out" oval or triangular ulceration characterizing the acute ulcer, stage 3. Arrow points to area from which the photomicrographs shown in Figure 6a and b were taken.

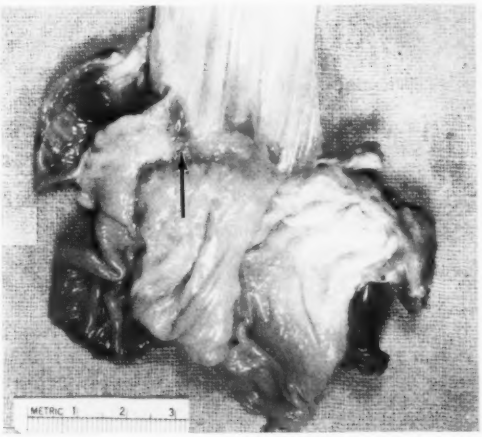

FIG. 7.

centimeters of the esophagus and occasionally extending throughout its entire length (Fig. 7). Microscopically, there is ulceration with destruction of the epithelium, lamina propria, and, occasionally, deeper layers (Fig. 6a). The superficial portion of the base of the ulcer displays an exudate comprised of polymorphonuclear leucocytes and fibrin. Occasional plasma cells and eosinophils are visible. A cellular type of early granulation tissue may be present with dilatation of the capillaries (Fig. 6b).

Stage 4a. Grossly, there are ulcers with rolled and irregular margins which tend to become confluent. The base has a yellowish pink coloration, and the ulcer varies in shape, extent, and depth. In general, this type of ulcer (Fig. 8) is more shallow than those classified as Stage 3. Microscopically, there is loss of epithelium with chronic inflammation of varying depth together with dense, cellular granulation tissue and a predominance of lymphocytes (Fig. 9).

Stage 4b. Grossly, this stage has pinkish yellow, nondepressed streaking or patchy areas. Microscopically, fibrous connective tissue is found to be in the process of replacing the cellular granulation tissue. The over-

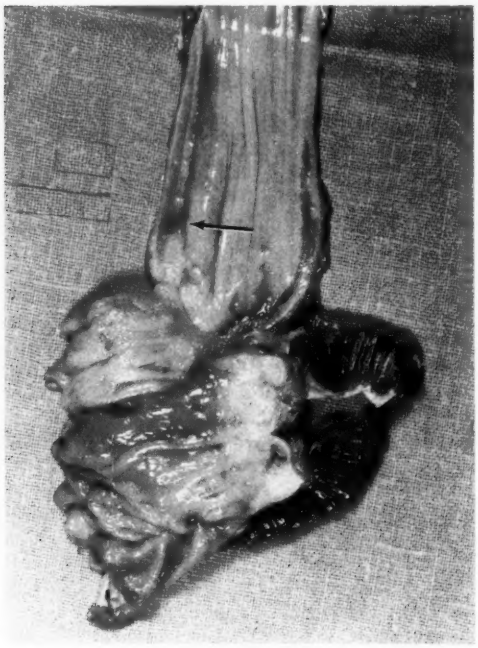

FIG. 8. Gross specimen of dog sacrificed at 20 months. Irregular confluent streaking ulcerations with irregular rolled margins and bases of varying depth are seen which characterize chronic esophageal ulceration, stage 4a. Arrow indicates the site from which the photomicrograph of Figure 9 was taken.

lying epithelium may be thin or, in the more advanced stage of healing, there is a thickened-appearing normal epithelium with thin, filmy fibrous tissue immediately subadjacent (Fig. 10).

There may be in both stages a and b varying degrees of acanthosis, thickening of the duct epithelium, and follicular collections of lymphocytes in the lamina propria or submucosa (Fig. 11).

Suture granuloma. In the process of studying reflux esophagitis, a type of acute and chronic granulation tissue which surrounded the silk sutures was frequently identified. The granuloma presented an appearance which was different from the inflammatory reaction initiated by the reflux of gastric juice. Grossly, these granulomas are small, round, pink elevated areas. Microscopically, there are collections of polymorphonuclear leucocytes in the early stages with chronic inflammatory cells dominating later. This type of reaction was confined to the area where the remains of the suture material could be identified and usually was localized in a circumferential manner around this foreign body. Catgut sutures generally did not present this reaction. In any event, these granulomas had no influence on the development of reflux esophagitis which could always be identified as a separate and distinct entity.

Infection. In one animal, the esophagus on gross inspection displayed a diffuse red appearance extending up to the pharyngoesophageal junction with gangrene near the suture line. Microscopically, there was hemorrhage and gangrene at the suture line with marked dilatation of the blood vessels in the lamina propria and submucosa without inflammatory infiltration of the remaining esophagus. Thus diffuse erythema, as seen in this animal, differed from the beefy red streaked appearance seen in reflux esophagitis. In another animal which exhibited stage 3 esophagitis an ascending lymphangitis was also displayed as a separate entity in the connective tissue between the submucosa and muscularis externa.

For the most part, the progressive picture of reflux esophagitis was determined after study of animals which had been subjected to the type A operation wherein the junctional esophageal segment was excluded and an esophagogastrostomy created through the hiatal canal. It is interesting to note that in the permanently inverted pouches (type B) in which changes were severe, progressive, and diffuse, ulceration though not observed grossly could be identified microscopically. In the middle esophageal pouches, the grossly visible localized and deep ulcers were due, we believe, to the jetlike entry of gastric juice from the stomach into the pouch. In those dogs in which the lower esophageal segment was returned to its normal position after the development of esophagitis (type D), the gross appearance was completely normal at the time of sacrifice. The microscopic sections also, for the most part, were entirely

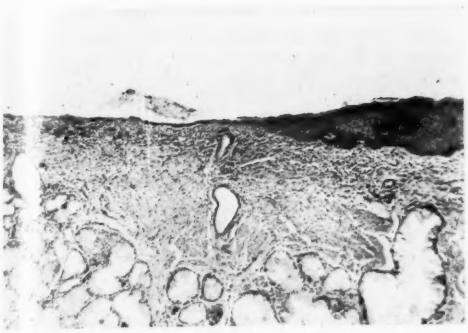

FIG. 9.

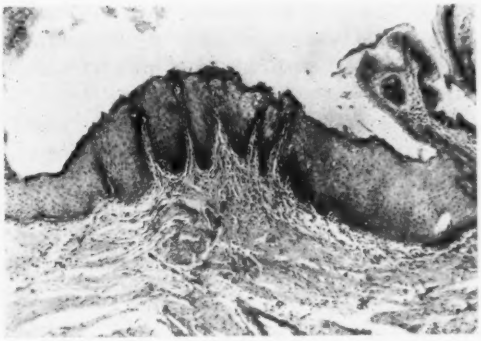

FIG. 10.

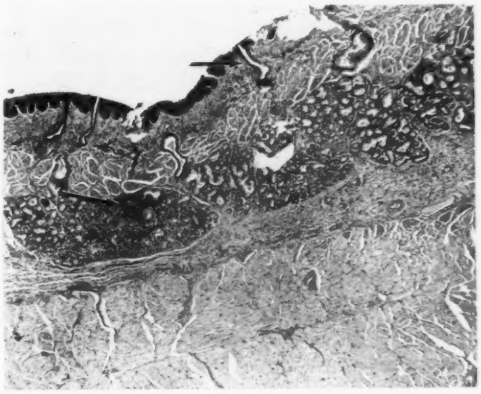

FIG. 11.

FIG. 9. The base of the ulcer is at the same level as the adjacent epithelium; compare with Figure 7. There is loss of epithelium with superficial destruction of the lamina propria and cellular granulation tissue in the base of the ulcer, stage 4a. ×50.

FIG. 10. Thickening and acanthosis of the epithelium with an underlying filmy fibrous tissue denote a late stage of healing, stage 4b. ×50.

FIG. 11. Section from a grossly normal area of the esophagus shows thickening of the duct epithelium, right arrow, and collections of lymphocytes in the glandular area, left arrow, stage 4a and b. ×18.

normal. However, in some areas a normal epithelium overlay a filmy fibrous tissue indicating that almost complete healing had occurred (Fig. 10).

In one instance in which the animal was sacrificed at the end of 7 days, both gross and microscopic ulceration was noted; a stage 3 acute ulcer was present as well as stage 4b changes which indicated that the entire cycle had evolved in the 7 day period. In a dog sacrificed at 5 weeks, the esophagus was grossly normal but patchy necrosis of the epithelium with loss of nuclei was present upon microscopic examination (stage 1). On the basis of such examples, it might be theorized that there are inherent dissimilarities in the resistance of the esophageal mucosa in different animals and in various areas of the esophageal mucosa in the same animal. In a previous study, there was no definite correlation between gastric acidity and the severity of the esophagitis (2). Many animals showed more than one stage of the disease process at the same time. Stage 1 changes in the epithelium over a healed stage 4b lesion were not observed which gave the impression that progression of the disease may occur by successive involvement of new areas.

DISCUSSION

Ripley, Olson, and Kirklin in a 16 year study of patients undergoing operations on the esophagogastric junction found that in 40 of 65 patients esophagitis developed at intervals from 2 months to 4 years after operation. This and other clinical reports indicate the need for a better understanding of the etiology, pathogenesis, and operative prevention of this disease. Our initial work

confirmed the presence of a lower esophageal intrinsic sphincter which is of prime importance in the prevention of esophageal reflux (2).

To date, no definite experimental studies have been made which focus on the sequential pathologic changes which occur during the development of postoperative reflux esophagitis. From a clinical standpoint, knowledge of these changes is necessary in making decisions regarding medical and surgical therapy. This controlled experimental study of esophagitis which simulates that found clinically after operation on the gastroesophageal junction provided the opportunity to study the pathogenesis of reflux esophagitis.

Lodge performed a study on esophagi obtained from 600 autopsies. The incidence of esophagitis was 30 per cent in 500 cases of random necropsy specimens and 8 per cent in 100 cases of sudden death. Microscopic sections were taken from the lower third of the esophagus, regardless of whether or not there was gross evidence of esophageal disease. The progressive changes which Lodge described emphasize the depth of esophageal wall involvement. This was the first attempt to categorize the gross and microscopic pictures which, based on her study, were classified essentially as follows:

Stage I showed little or no macroscopic change, but the microscopic picture showed an intact epithelium with infiltration of the lamina propria with polymorphonuclear leukocytes and plasma cells. There was no frank ulceration but occasional epithelial desquamation. Capillary dilatation was noted in the lamina propria and submucosa. There was no inflammatory cellular infiltration in the submucosa. Stage II macroscopically showed injection of the mucosa with opacity and roughening together with tiny ulcers. Diffuse pink streaking was sometimes seen. Microscopically the ulcers were shallow and discreet with the base extending through muscularis mucosa. Inflammatory cells were present in all layers except the muscularis externa. Stage III macroscopically revealed that the ulcers had become numerous with ill-defined margins tending to coalesce and extending through the muscularis externa. Microscopically there were large areas of denuded epithelium with increased inflammatory infiltration of the submucosa with extension of the ulcerative process to the muscularis externa. The differentiation of chronic from acute esophagitis often could not be made by the naked eye. Microscopically fibrosis was seen in the lamina propria and sometimes extended to the submucosa.

Peters in a similar study of material from 114 autopsies separated the disease into acute and chronic forms without attempting a more refined analysis in staging the disease. In general, the pathologic findings coincide with those of Lodge. Simultaneous occurrence of acute and chronic inflammation was also noted by Peters.

From a study of biopsy specimens taken at esophagoscopy in 61 patients, 12 of whom had serial biopsies at varying intervals, Palmer concluded that the inflammatory process starts deep in the lamina propria and spreads superficially toward the epithelium. This opinion was based on the fact that the serial biopsies showed little pathologic change and, frequently, an intact overlying epithelium was seen with inflammation in the lamina propria. Hence, he surmised that peptic esophagitis is not caused by corrosive action of regurgitated gastric juice.

It would appear from our work that reflux esophagitis follows a definite sequential pattern starting with epithelial destruction. We have observed an earlier stage than Lodge which shows only necrosis of the epithelium (Fig. 2a). In our stage 1, inflammatory cells are not seen in the esophageal wall since the gastric juice has not yet pierced the protective barrier of the epithelium. In Stage 2, the inflammatory changes are now present in the lamina propria and, occasionally, the submucosa since the protective epithelium has been destroyed by the gastric juice. Although for the most part the epithelium has been lost, areas of epithelial regeneration indicate that the process may stop at this stage and healing may occur. Stage 3 indicates progressive damage by the gastric juice with acute ulcer formation, and then proceeds to chronic ulcer formation or healing. Acute and chronic ulceration can usually be differentiated macroscopically (Figs. 7 and 8). Since we have observed different

stages occurring simultaneously in the same animal, we believe that the esophageal mucosa is injured by the regurgitant gastric juice at different times, although the reason for this is not yet apparent. In the healing stage, stage 4b, necrosis of the overlying epithelium has not been detected which suggests that healed epithelium has an increased resistance to gastric juice.

One of the problems encountered clinically with severe reflux esophagitis is that of occasional stricture formation. However, with the procedures we have utilized in this experimental study, this late complication did not develop in any of our animals.

The impressions gained by esophagoscopy are often misleading. However, certain generalizations can be made. If the mucosa has a beefy red appearance or displays discreet ulceration, the disease probably corresponds to stage 3. If the appearance is a patchy or diffuse pinkish or yellowish red through the endoscope, the pathologic changes are likely to be a chronic ulcer, stage 4a, or early healing of the chronic ulcer, stage 4b. Because a chronic ulcer appears as a shallow nodular area, it is often missed endoscopically. A grossly normal mucosa may, on microscopic section, reveal early evidence of esophagitis, stages 1 and 2, or late healed stage of esophagitis, stage 4b. We believe that gross changes in stage 2 cannot be detected because only small isolated areas of epithelial loss occur scattered within large areas of normal epithelium.

SUMMARY AND CONCLUSIONS

Reflux esophagitis was developed in 29 dogs by surgical interference with the normal closing mechanism of the gastroesophageal junction. A controlled histopathologic study of reflux esophagitis was made. The animals were studied for from 1 week to 20 months. From detailed gross and microscopic analyses, the pattern of development of the disease process became apparent. Sixteen animals displayed more than one stage of the disease and, in 12, only one stage was identified. In 2 animals, infection developed which was recognized as a distinct process separate from reflux esophagitis. Suture granuloma also was shown to be an isolated entity.

The following conclusions were reached:

1. Reflux esophagitis proceeds through a sequential pattern of destruction and healing.

2. The histopathologic characteristics of this disease are best described by 4 stages: epithelial necrosis, stage 1; loss of epithelium with scattered inflammatory cell infiltration in the lamina propria, stage 2; acute ulceration with destruction of the normal architecture of the mucosa alone or together with the submucosa, stage 3; and finally, chronic ulceration, stage 4a, which may persist if extensive or may heal completely, stage 4b.

3. This classification provides an accurate method to evaluate and compare the efficiency of reconstructive procedures on the esophagogastric junction if this area must be disturbed by operation.

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THE FLOOR AS A RESERVOIR OF HOSPITAL INFECTIONS

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THE FLOOR, the largest horizontal surface to accommodate settling bacteria, cannot be ignored epidemiologically. Floor cultures are excellent indicators of the bacteriologic types of infection prevailing, reflect qualitatively and quantitatively the bacteriology of the room's occupant, and are an index of the infectivity of the environment.

In this study, migration of a particular staphylococcus with a specific phage type has been traced from 3 small carbuncles on an otherwise healthy-appearing woman through the air onto the floor. Conversely, a carrier of a specific phage-type staphylococcus has been located by identifying the organism on his living room floor.

These studies led to an investigation of the dynamics of spread of bacteria in a hospital. Description of areas heavily contaminated by hospital strains of bacteria and the interrelationship of the organisms recovered from the environment and carriers inspired the conviction that definition of a hygienic hospital environment would be a major contribution toward the suppression of hospital-acquired infections. The observations reported herein were selected to depict the role of the floor in the dynamic system that disseminates microbes throughout an environment (2). These data involve 37,000 individual cultures which demonstrate the bacteriologic climate of a particular hospital in which adult patients of widely varying types were cared for by personnel outnumbering them 5 to 1 and in which unlimited visiting hours were permitted. So many variables are operative that analysis of the data is too tedious and bewildering for presentation in a periodical. Examples demonstrating the parameters of the experience are therefore reported as these relate to the role of the floor as a reservoir for microbes. Other components of the ventilation vortexes that surround human activities will be described in subsequent articles. Ultimately, the interrelationships between the floor, the clothing-bedding-laundry cycle, the air-conditioning cycle, and the infectious environment will be documented.

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MATERIALS AND METHODS

Three types of bacterial samples were made in these studies: settling, air-borne density, and floor cultures.

Settling, or fall-out, of bacteria was determined by exposing standard petri dishes containing horse blood agar for definite periods. A standard 10 centimeter petri dish has an area of approximately 1/15 square foot; hence, a 15 minute collection represents the average number of air-borne, bacteria-laden particles settling out per square foot per minute.

Air-borne density of bacteria, or volume air sampling, was done with the Wells air centrifuge. The flow was regulated so that 1 cubic foot of air was aspirated per minute. Samples were taken for 5 minutes; therefore, counts represent bacteria-containing particles in 5 cubic feet.

A colony grown from an air sample may represent many bacteria carried on a single particle. This was demonstrated by vigorously shaking air samples taken into buffer to disperse the bacteria prior to plating. Air samples in this study which produced 100 colonies in the air-centrifuge tubes actually yielded an average of 1,300 bacteria upon dispersal. Each colony, therefore, represented seeding by an average aggregate of 13 individual organisms.

Floor cultures were taken by thoroughly swabbing a 5 centimeter square area demarcated by a sterile aluminum template for 30 seconds with a sterile swab moistened in Butterfield's buffer. The swab was then shaken in 5 milliliters of buffer, and duplicate 1 milliliter samples were plated. The pour plate, thus, represents the bacteria removed from 1 square centimeter of floor. Floors which had been flooded with germicidal detergents were cultured into the appropriate buffered inactivator to prevent germicidal action during the procedure. The validity of this technique for culturing bacteria from the floor is demonstrated in Table I. Residual bacteria in the demarcated area were picked up by immediate successive swabbing with 4 additional swabs. The first swab picked up, on the average, 71 per cent of the total organisms which could be recovered in 5 successive samplings. The initial culture is sufficiently representative, therefore, to indicate the degree of bacterial contamination of the floor.

TABLE I.—NO. OF ORGANISMS PER SQUARE CENTIMETER OBTAINED AT SUCCESSIVE SWABBING OF A DEMARCATED AREA OF FLOOR TO DEMONSTRATE VALIDITY OF SAMPLE

Area	*Swab 1*	*Swab 2*	*Swab 3*	*Swab 4*	*Swab 5*
A.	690	150	370	5	1
B.	7	1	1	1	2
C.	89	6	2	1	3
D.	15	4	4	0	0
E.	7	3	0	0	0
F.	7	1	0	0	0

TABLE II.—BACTERIAL FALL-OUT IN CONTAMINATED PARTICLES PER SQUARE FOOT PER MINUTE DURING PERIODS OF MINIMAL ACTIVITY

Location	*Bacterial fall-out*	*Settling velocity**
Laundry		
Sorting area (classification)	300	3.78
Other areas	9	1.69
Ward (14 bed)		
During bedmaking	50–260	2.20
No activity	15– 50	2.20
Isolation with air conditioning	2	1.42
Isolation with fan pulling in outside air	4	2.04
Isolation with fan exhausting room air	6	0.77
Operating Room		
Hospital A	7–10	0.85
Hospital B	7	1.00
Hospital C		
Operating suite	2–5	1.07
Isolated specialty operating room 1	61–92	—
Isolated specialty operating room 2	12–37	—
Operating room corridor		
Center	7	—
Side	3–11	—

*Feet per minute.

RESULTS

Bacterial fall-out during periods of average activity in different hospital areas has been determined as shown in Table II. During activity hours, many times the number of particles listed settle on each square foot of exposed floor. In a busy hospital corridor, for example, the daily total fall-out is 1,400 times the single observation. The laundry count must be multiplied by 400 to yield the fall-out of a 7 hour workday. The activity factor in a single room is about 100; in an operating room, about 50. The activity factor was estimated by studying the daily use of each area. For example, traffic counts in a corridor revealed wide variations in the activity that causes bacterial turnover from the floor. During peak hours, 2,000 feet scuffed up dust; and doors were opened 800 times with resultant change in air currents to whisk dust into the air. During slack, early morning hours, activity fell to 50 feet with 25 door openings. It was shown that during 1,400 minutes of the day bacterial turnover occurred, and dust and bacteria were simultaneously resuspended and settled out. These bacteria represent redistribution of settled dust plus new increments from people and equipment. A floor culture taken simultaneously with the 300 fall-out figure in the laundry showed 12,000 organisms per square centimeter, or approximately 12×10^6 per square foot. This represents the cumulative total of viable bacteria available for air-borne dissemination.

The relationship between the bacteriology of the floor and the infected occupant was demonstrated by the admission of a

FIG. 1. High air-borne counts were traced to accumulated soil beneath a cystoscopic table that had not been moved for cleaning. Disinfection of total floor area resulted in hygienic air.

patient with 3 small carbuncles to a disinfected room. The staphylococci, phage type 79, isolated from the lesions, nasal fossae, skin, and anus were alien to the hospital. Dissemination of the bacteria was traced (3). Table III illustrates the accumulation of these specific staphylococci on the floor of the room.

TABLE III.—PHAGE 79 STAPHYLOCOCCI COMMON TO CARBUNCLES, NASAL FOSSAE, SKIN, AND ANUS RECOVERED FROM AIR AND FLOOR UPON ADMISSION OF PATIENT TO DISINFECTED ROOM

Date 1958	*Total floor counts, organisms/cm.²*	*Total volume air counts, organisms/5 ft.³*
Jan. 2	6	36
	PATIENT ADMITTED	
Jan. 3	58*	100*
Jan. 6	30	44
Jan. 8	81	190
Jan. 9	52	160

*Sixty to 70 per cent of all counts after January 3 are Staphylococcus aureus, phage type 79.

TABLE IV.—ACCUMULATION OF BACTERIA IN THE ROOM OF A STAPHYLOCOCCUS, PHAGE 77, CARRIER AIR COUNTS DURING BEDMAKING

Date 1958	*Fall-out**	*Volume†*	*Settling velocity‡*
Jan. 30		ROOM DISINFECTED	
Jan. 31	5	27	1.0
Feb. 3	17	37	3.8
Feb. 7	19	57	3.5
Feb. 11	23	100	2.3
Feb. 18	63	200	3.0

Eighty-five to 90 per cent Staphylococcus aureus, phage type 77.
*Bacteria-laden particles per square foot per minute.
†Bacteria-laden particles per 5 cubic feet.
‡Particles in feet per minute.

Routine floor cultures of 40 rooms in the resident staff's quarters showed an average count of 85 bacteria per square centimeter with a median count of 26 and a standard deviation of 165. One room yielded a count of 2,000 per square centimeter, predominantly staphylococci, phage type 77. Cultures of the room's occupant revealed high counts of this staphylococcus in his hair, nasal fossae, skin, and clothing.

The accumulation of bacteria in this room was studied. Bedding, draperies, rug, and personal effects were sterilized in an ethylene oxide sterilizer. The walls and furniture were washed with a long-acting germicide, and the floor was flooded with a germicidal detergent. The excess was removed by a wet-pickup vacuum cleaner. Subsequent cultures are shown in Table IV.

These staphylococci were shed from a healthy-appearing individual with no patent respiratory tract or skin infection. The data differentiate him quantitatively from 38 other residents. The bacterial counts of these 38 men and their quarters were low. The remaining man, a carrier of staphylococcus, phage type 80/81, had 2,100 organisms per square centimeter on the floor from which staphylococcus, phage type 80/81, was recovered. Because this was a prevalent strain in the hospital flora at the time, accumulation studies were not done.

Floor cultures have exposed problem areas; for example, bacterial counts on the floor in a cystoscopy room were consistently high despite daily disinfection. Figure 1 shows debris found under the cystoscopy table which had not been moved to permit cleaning of the floor. Once this area was cleaned, floor counts elsewhere in the room fell and have remained below 5 per square centimeter.

The floor has 3 extensions that are of utmost importance to hygiene. Coves, stairs, and walls of elevator shafts share an attraction for spitters. The air currents prevalent

in stair wells and shafts disseminate bacteria widely. Footstools and bed steps also accumulate bacteria. These surfaces are seldom cleaned.

Cultures of the wall of an elevator shaft in a private pavilion gave bacterial counts of 240 and 120 organisms per square centimeter. Coagulase-positive staphylococci, phage types 79/42D/7/42E/47/53/77/42B/VA4/81/44A, and enterococci were recovered. Another elevator shaft leading to the surgical ward yielded 8 and 33 organisms per square centimeter with an occasional coagulase-positive staphylococcus which was nontypable.

Cultures taken in areas in which trash cans were being emptied into a truck and near laundry chutes as the unbagged soiled linen was being transferred to a truck yielded the data shown in Tables V and VI. Volume air counts are doubled when wastebaskets are emptied and increase tenfold during handling of soiled linen. Figure 2 illustrates the bacterial contribution to the air by the latter. These data illustrate the dispersal of bacteria which results from commonplace activities and the ultimate settling on the floor of the majority of the bacteria. A high proportion of coagulase-positive staphylococci was found in all cultures—air, floor, and settling plates.

Figure 3a shows the results of a series of floor cultures done in an operating room in which an ordinary soap solution was used for floor cleaning. The clean mop and clean pail of solution were effective initially; but, as the washing progressed, dispersal of the bacteria removed from the floor in the wash water reached the point where the incremental addition to the mop and pail became so great that more organisms were spread than were removed. When the pail was emptied and refilled with fresh soap and water, the mop transferred enough bacteria to the clean water to make the total number of organisms uncountable. Cultures of a sterile mop, pail, and soapy water immediately after replacing the mop after its use on a floor and at the end of a week-end

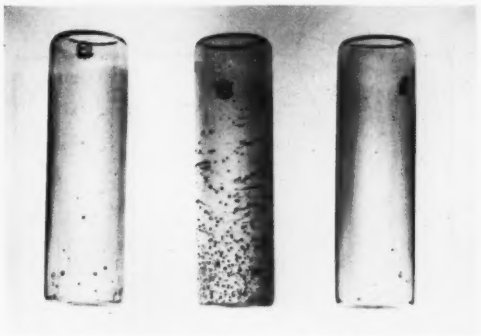


FIG. 2. Air-borne bacteria captured from corridor air in a Wells air-centrifuge tube aspirating 1 cubic foot per minute for 5 minutes before (a), during (b), and 5 minutes after (c) pulling soiled laundry. The majority was coagulase-positive staphylococci.

storage in a janitor's closet were 230 per milliliter and 19×10^4 per milliliter respectively.

Figure 3b shows the bacterial counts in the same operating room after it was cleaned by a technique which was developed to provide effective concentration of germicide and insure the removal of residual slurry. The counts are all in single digits. No change had been made in the cleaning personnel. During a 15 month period, 386

TABLE V.—CULTURES TAKEN BEFORE, DURING, AND 5 MINUTES AFTER TRASH COLLECTION

	Air samples (5 cubic feet)			*Particles settling (1 square foot/min.)*		
Area	*Before*	*During*	*After**	*Before*	*During*	*After**
F_2.....	250	480	80	36	120	33
F.....	55	160	100	9	72	84
E.....	130	350	120	30	42	48

*All "after" samples taken after lapse of 5 minutes.
N.B. Sixteen per cent of all organisms were Staphylococcus aureus, coagulase positive.

TABLE VI.—CULTURES NEAR LAUNDRY CHUTE

	Air samples (5 cubic feet)			*Particles settling (1 square foot/min.)*		
Chute	*Before*	*Pulling laundry*	*After**	*Before*	*Pulling laundry*	*After**
A.....	26	260	85	33	480	63
C.....	45	1500	27	33	140	87
D.....	77	160	34	15	330	27
E.....	47	330	54	—	180	54
F.....	75	700	60	110	420	45

*All "after" samples taken after lapse of 5 minutes.
N.B. Seventy per cent of all organisms were Staphylococcus aureus, coagulase positive.

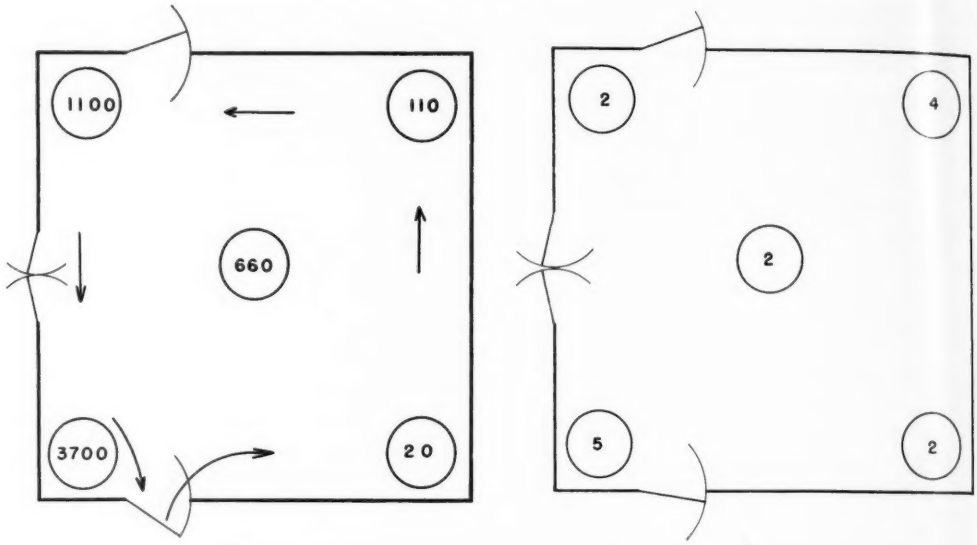


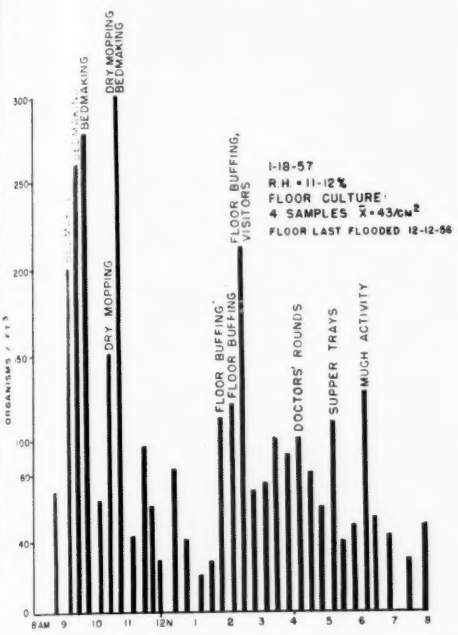
FIG. 3. a, Plot of floor cultures of operating room taken after conventional mopping of floor with soapy water. O indicates bacteria per square centimeter and → indicates mopping sequence. b, Floor cultures of same areas made after disinfection by flooding with germicidal detergent. O indicates bacteria per square centimeter.

cultures were made to monitor the effectiveness of the cleaning program. Fifty-four per cent of the counts were 5 or lower; 74 per cent, 10 or lower. The germicidal detergents used included iodophors, phenolics, and quaternaries.

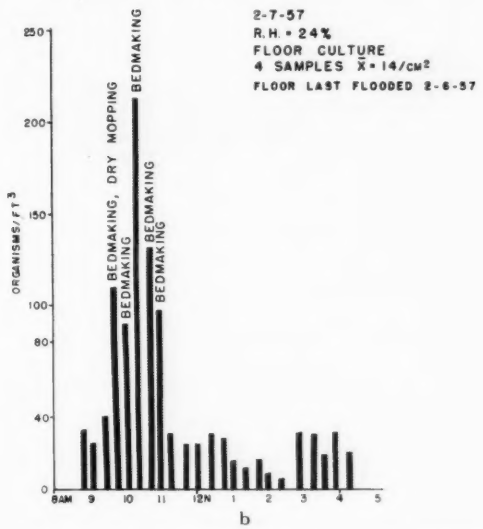
The results of a 6 months' study using different germicidal detergents in each operating room were as follows: synthetic phenolic was rated 1, iodophor 2, quaternaries plus Na_3PO_4 3 and 5, and quaternaries 4 and 6. Floors were ranked each day: The lowest bacterial count was rated as 1; the highest, 6. Analyses of the results of ranking are included in our study. This method eliminates the undue weight that one unusually high count could have on a simple mean calculation of the coefficient of concordance; then, testing it for significance by using Snedecor's distribution for F,[1] described by Moroney, yields a P of .01, indicating a significant degree of agreement in the ranking of the different germicidal detergents.

The same technique of floor washing when used in the wards reduced the volume air counts. Figure 4a shows the number of bacteria-carrying particles in volume air samples in a 14 bed surgical ward. The floor had been cleaned once, 1 month previously, by the new technique. Peaks occurred at bedmaking and dry mopping. The base count when there was no activity was about 40 bacteria-laden particles per 5 cubic feet of air. The bacteriology represents, therefore, 1 month's accumulation resuspended by air currents and ward procedures. Figure 4b shows the results of air sampling in the same ward 1 day after the floor had been cleaned by the new method. Bedmaking and dry mopping did not raise the volume air counts proportionately, and the base count with no activity was approximately 18 particles. The accumulation of bacteria on the floor on the days after cleaning is shown in Table VII. Since this

[1]F = Variance ratio test. (Ratio between two variances used to test for significance; named F by Snedecor in honor of R. A. Fischer.)



a



b

FIG. 4. a, The number of bacteria-laden particles (75 per cent micrococci) in the air in a surgical ward related to activity. The floor had been disinfected 1 month previously. b, Activity does not scuff bacteria-laden particles (50 per cent micrococci) from floor in the same ward disinfected 24 hours previously.

14 bed surgical ward was completely occupied, daily dry vacuuming had to be done to maintain gross cleanliness.

The bacterial population on the floor can be reduced by vacuum cleaning. Cyclonic separator types of cleaners, with discharge filters and diffusers which avoid a trailing jet of air that raises dust and bacteria from the floor, were used to demonstrate the effectiveness of this method. The asphalt tile floor in a 14 bed surgical ward was cultured before and after vacuum cleaning. Bacteria were cultured from contiguous areas in 10 locations about the floor and the comparable pairs of cultures yielded are listed in Table VIII. A statistically significant reduction in bacteria was demonstrated; moreover, air samples taken simultaneously with dry vacuuming or floor flooding techniques have never shown a rise in bacterial count.

Evidence that hospital soil protects organisms that settle on the floor is shown in Figure 5. Staphylococcus aureus, phage type 80/81, isolated from a patient with osteomyelitis was mixed with equal amounts of amniotic fluid and blood. The mixture was spread on 4 common types of surfaces —glass, conductive linoleum, vinyl tile, and asphalt tile. A distilled water suspension of the same organism was spread on another set of identical surfaces as a control. The

TABLE VII.—ACCUMULATION OF BACTERIA ON WARD FLOOR AFTER FLOODING (ORGANISMS PER SQUARE CENTIMETER)

Date *1959*	*Mean**	*Median†*
March 31	FLOOR FLOODED	
March 31	31	3
April 1	26	13
April 2	37	15
April 3	11	8
April 6	65	39
April 7	89	26
April 8	18	9
April 9	18	13
April 10	65	7
April 13	76	36
April 14	85	50
April 15	140	87

Floor flooded March 31, 1959; thereafter dry vacuumed daily, no wet mopping except in small areas to pick up spillage.
*Average of 14 samples, each done in duplicate.
†Median of 14 samples, each done in duplicate.

FIG. 5. Human soil preserves bacteria on flooring of hospital.

staphylococci could not be recovered from the control surfaces after 8 hours, while appreciable numbers were recovered from the tiles spread with staphylococcus amniotic fluid and blood mixture after 24 hours.

Floor waxes containing germicidal agents have been tested by application on a ward and a corridor floor. The method of testing consisted of applying the waxes in wide bands across a scrubbed, freshly stripped asphalt tile floor. Control areas were left bare. Cultures were taken daily in 3 places on each band for the period of the test. Dry vacuuming was done daily. A rating system, previously described, was used to analyze the data. It was not possible to get reproducible, statistically significant results from 5 sets of such experiments, 4 of which were done during a 2 week period; 1, during a period of a month.

DISCUSSION

Patients with infection continually shed microbes into the environment. These organisms may be carried in droplets, droplet nuclei, or on particles of dust. The size of these forms has been defined as: droplets, larger than 100 microns; dust particles, 10 to 100 microns; droplet nuclei, 2 to 10 microns.

Droplets settle immediately to the floor. Dust particles also drift to the floor, their settling velocity depending upon the size of the particles. Droplet nuclei, the smallest of the 3, do not settle to any appreciable extent, although even some of these may eventually be deposited upon the floor. Droplet nuclei are more likely to float about on air currents until inhaled or removed by natural or mechanical ventilation. Particles containing bacteria remain on the floor until stirred up by activity and air current. The latter may be imperceptible.

Because bacteria accumulate on the floor, the method of floor care employed is the major factor determining the fate of this bacterial debris. Unless these organisms are destroyed at frequent intervals, floor counts

FIG. 6. Operator is using a wet-pickup vacuum cleaner in order to remove the slurry of soil and the residual germicide.

FIG. 7. Floor washed with dirty mop water to which glove powder was added to show imperfections in floor where slurry pools.

reach astronomic proportions; and air counts are concurrently increased. The effectiveness of germicides which impart persistent bactericidal activity to surfaces has been considered in this study. All of those used were effective in this regard in the laboratory, particularly when tested against aerosols of bacteria. Under extremes of relative humidity and in the presence of infected hospital dust, particularly from textile fibers, removal of the dust and bacteria by cleaning is more effective in decreasing volume counts of airborne bacteria than germicidal treatment of surfaces alone.

The settling velocity of the bacteria-bearing dust can be estimated by collecting volume air cultures and settling plates simultaneously. The area count per square foot divided by the volume count per cubic foot is the settling velocity in feet per minute.

Studies in the operating room have shown that the mean settling velocity of bacteria-laden particles is 1.04 feet per minute (average of 18 experiments). The mean settling velocity on a ward is 2.19 feet per minute (average of 27 experiments). Analyses of the data showed the difference to be highly significant with a probability of less than .01, using the t^2 test. In the room of a staphylococcus carrier, a mean settling velocity of 2.72 feet per minute was found. Because droplet nuclei have been calculated to have a settling velocity of less than 1 foot per minute, the velocities cited indicate the settling of dust particles.

Experience in environmental bacteriology has shown that organisms associated with staphylococcal infections are found in particles of rapidly settling velocity. These particles settle out on any horizontal or sloped surface. The floor is the largest horizontal area and cannot be ignored epidemiologically.

The ineffectiveness of conventional methods of floor care has been demonstrated by bacteriologic study. Dry mopping and dry sweeping result in high air counts; moreover, mops and brushes become heavily loaded with bacteria. The conventional mop, pail, and soapy water method does not disinfect and may coat the floor with a thin dispersal of organisms. The wet mop and residual slurry in the pail become a culture medium. The dirt, pus, blood, excreta, soap, and water combination yields in a few hours a bacterial population comparable to a 24 hour broth culture. The mop pail is a great bacterial multiplier and reservoir.

TABLE VIII.—BACTERIA PER SQUARE CENTIMETER ON A WARD FLOOR BEFORE AND IMMEDIATELY AFTER VACUUM CLEANING

Area	*Organisms/cm.*[2] *Before*	*Organisms/cm.*[2] *After*
1	3	2
2	11	1
3	38	3
4	8	1
5	2	1
6	6	2
7	8	3
8	81	2
9	6	3
10	40	3

P is less than 0.05*t* test.
P is .001 sign test.

The following method is recommended for daily floor care of the operating room: After each procedure, the center of the floor is mopped with a 3 inch string mop, wet with a fresh solution of a germicidal detergent. The mop is rinsed thoroughly in running water after each use and is sent to the laundry at the end of the day. Because it is easily cleaned, a flushing rim service sink is more satisfactory than a pail for dilution of the germicide and care of the mop.

A sanitary floor is essential to control airborne contamination. Provision of facilities for disinfection of the floor in the substerilizing room adjacent to the operating room is as important to asepsis as the instrument sterilizer.

At the end of the day's schedule, all furniture is removed from the room so that the entire floor is accessible for cleaning. Trash and debris are picked up with a water trap or cyclonic separator type vacuum cleaner. A germicidal detergent solution is freshly made in a clean, 12 quart pail. The formula-

[2]*t*, also known as student's t distribution, used as a test of significance for small samples. (See *Tables for Statisticians*, Arkus & Colton, Barnes & Noble, Inc., 1950.)

tion should contain either a quaternary, a phenolic, or an iodophor in sufficient concentration to be bactericidal on the floor to be cleaned. This concentration must be determined by experiment. The actual germicide used is less important than how it is applied. Open shelves, moldings, window sills, overhead lights, furniture, and other horizontal surfaces are wiped with a clean cloth which has been wrung out of the germicidal detergent solution. One quart of the solution is spilled over the area of the floor likely to have been soiled with blood, pus, or amniotic fluid. The contaminated area is scrubbed with a clean 3 inch cotton string mop to loosen soil. The remaining 11 quarts of germicidal detergent is spilled on the scrubbed area and spread with the mop to the periphery of the room. Obvious soil spots are solubilized as necessary. This exposes the area of maximal contamination to effective concentrations of germicide. The cove is scrubbed with the mop as the cleaning solution is spread to the periphery of the floor. A pattern of distribution of the solution begins at the left of the door facing the corridor and follows the periphery of the room to permit the worker to encircle the flooded center as he spreads the germicidal detergent in his peripheral retreat to the door. The slurry is removed with a wet pickup vacuum cleaner. This advance begins at the door so that the hose and vacuum cleaner remain clean and dry. A puddle of germicidal detergent is deposited across the doorway so that the casters of the furniture are deliberately run through germicide as the furniture is returned to the room.

This technique is recommended for daily care of the floor in nurseries and isolation areas. It should be used for terminal disinfection of patient care areas. A scrub machine that automatically dispenses the germicidal detergent is timesaving and convenient for large floor areas.

Most germicides have inherent properties that interfere with their bactericidal action. Substantivity, reactivity with organic matter, saponification with hard waters, or chemical incompatibility diminishes germicidal power; thus, the water, the mop, the dirt and debris on the floor, and the flooring itself deplete the solution of its bactericidal power. An excess of germicidal solution must be used to leave a residual on the floor after satisfying the affinity of the floor, mop, and soil for adsorbable ingredients. Destructive concentration of detergent is avoided by using dilute solutions. There is a hidden advantage to the wet pickup technique. The slurry of dirt loosened from the floor by the cleaning solution is not easily overlooked. To remove the obvious water, the operator is forced to vacuum the entire floor, leaving it grossly clean (Fig. 6). Experience with dry vacuuming or wiping with a treated cloth demonstrates that only 60 per cent of the floor is cleaned because there is no demarcation of the cleaned area.

Another advantage of the wet pickup vacuum cleaner concerns worn floors. Floors several years old do not have plane surfaces (Fig. 7). Indentations, cracks, checks, chip craters, scratches, spalled areas, joints, and loosened tiles retain minute puddles of the cleaning solution and soil. Bacteria may grow in this accumulation. The motion of loose tiles under traffic pumps dust and bacteria from the reservoir beneath them. The wet pickup technique removes the residual puddles more effectively than any other method.

Labor standards have been developed for this technique. A team of 2 men works most effectively when sharing the operation of moving furniture, picking up litter, spreading the germicidal detergent from a pail, and vacuuming. With the flooding technique, the standard is 800 square feet per man hour. Substitution of a dispensing scrubber permits a standard of 930 square feet per man hour. The greatest waste of time results from interference by the professional staff. In one study, half the cleaning time was wasted in waiting. A hygienic environment is a sufficiently important and expensive component of medical care to warrant scheduled periods for cleaning clini-

cal areas, respected by all and interrupted only for emergencies stemming from disease. Experience in industries in which air hygiene comparable to that desirable in hospitals is essential indicates that the cost of a floor cleaning program is 85 cents per square foot per year. The annual cleaning budget should approximate $170 per bed.

The choice of a germicidal detergent for floor care is critical and should be based upon in-use tests. Unfortunately, laboratory tests on floor disinfectants and germicidal waxes and oils, while indicating the presence or absence of bactericidal activity, do not approximate actual conditions of use. Laboratory testing ignores such factors as chemical and physical characteristics of the mops, the surface of the floor as it has been altered by scuffing, waxing, and wear, and the type of human soil and contamination that exist in the hospital. The only valid test of floor disinfection in the individual hospital is culturing after routine cleaning with the product under test.

Periodic bacteriologic monitoring of the floor is essential in maintaining high levels of routine performance and in revealing problem areas. Operating room floors can be maintained at 5 organisms per square centimeter or lower; ward floors, at 10 organisms per square centimeter or lower. In-use testing has yielded surprising data. Spillage of infectious material, careless collection of trash, sketchy cleaning, and contaminated air conditioners have been discovered through bacteriologic monitoring of the floor.

There is a deep-seated prejudice against the use of vacuum cleaners in hospitals. Noise, ineffective cleaning, dissemination of bacteria, high maintenance costs, and inconvenience are cited as causes for their rejection. The patients' quiet is disrupted by noise from the pantry, elevators, page system, traffic, maintenance tools, hair dryers, radios, and televisions without the least concern. Scheduled cleaning is so important in preventing cross infection that this criticism cannot be entertained. Ineffective cleaning usually results from a plugged hose or a dirt-choked machine. The use of plastic hose which can be replaced easily eliminates the loss of suction due to kinks or the peeling lining of multilayered, built-up hose. Bag machines lose suction as the resistance of the accumulating dirt increases. Water trap or cyclonic separator machines maintain high levels of suction. Dissemination of bacteria results from whisking bacteria from the floor by the discharge jet. This can be eliminated, along with noise, by a properly designed diffuser. Studies demonstrating that bacteria penetrate the vacuum cleaner are based on the failure of new machines to filter out bacterial aerosols. A mechanically efficient, used machine rapidly becomes an effective filter for bacteria as dust accumulates. High maintenance costs reflect careless, even abusive, use of machines by inadequate personnel. Trained, purposeful cleaning teams recognize the value of appliances and tools in meeting performance standards with minimal fatigue.

Volume air counts do not increase during vacuum cleaning with properly designed, well maintained machines. Vacuum cleaners have been shown to be effective in removing bacteria-contaminated dusts and aerosols. The use of vacuum cleaners in place of all types of dry dusting and sweeping is recommended.

Floor waxes containing germicides were not found to alter floor bacteriology significantly over a period of time. They were, however, found preferable to waxes without such agents because of the danger of the wax itself becoming contaminated during storage. We have found waxes heavily populated with gram-negative organisms. Bacterial contamination of floor wax with staphylococci has been demonstrated. Application of such material resulted in dispersal of bacteria over previously disinfected floors.

Anyone responsible for maintaining cleanliness of floors recognizes the prevalence of spitting at random, negligence in cleaning up spillage of excreta and food, carelessness in discarding contaminated waste such as tissues, dressings, and perineal pads, and the

splattering of blood and parenteral medications. These kinds of human soil abet the survival of microbes in the environment. These behavior patterns constitute one of the basic problems in the control of cross infection.[3]

A hygienic environment results in disappearance of hospital strains of bacteria, a decrease in cross infection, and a shift of the bacteriology of the carrier toward the benign, both qualitatively and quantitatively.

RECOMMENDATIONS

1. Work teams should be trained to clean patient-care areas.
2. Properly designed machines must be supplied to permit the effective use of manpower.
3. Informed supervision is essential to enforce proper use of germicidal detergent and maintenance of machines.
4. Cleaning time must be scheduled and regarded as an integral part of patient care.
5. Bacteriologic monitoring of floor areas should be instituted to establish the in-use effectiveness of cleaning techniques.
6. Floors should be disinfected by the wet pickup technique on the following schedule: (1) daily disinfection of corridor, delivery room, dressing room, emergency ward, isolation room, nursery, pediatric ward, utility room, and operating room; (2) weekly disinfection of medical ward, surgical ward; (3) terminal disinfection of autopsy room, single room, and maternity ward.
7. Vacuum cleaners must be used in place of mops, brushes, and brooms in daily care of floors between periodic disinfection by a wet-pickup procedure.
8. Hospital procedures such as trash and laundry collection must be evaluated with the objective of minimizing dispersal of bacteria.
9. Do not spit at random is still an appropriate admonition.

[3]The reader's attention is directed to "Environmental Staphylococcal Contamination," *Lancet*, Lond., 1960 1: 670, by W. D. Foster. The article describes a method of assessing environmental contamination by staphylococci and its use in the investigation and suppression of an outbreak of staphylococcal wound infection.

SUMMARY

Bacteriology of the floor in several hospital situations is described. The bacteriologic effect of floor-cleaning methods is presented. In-use evaluation of germicidal detergents for floor care is described. The relationship between bacterial count on the floor and airborne bacteria is emphasized. A standard for a hygienic floor in hospitals is recommended.

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THE EFFECT ON RENAL FUNCTION OF OCCLUSION OF THE AORTA INFERIOR TO THE RENAL VESSELS

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IT IS OCCASIONALLY OBSERVED that after resection of aneurysms of the terminal aorta arising distal to the renal vessels, some patients exhibit varying degrees of renal dysfunction such as oliguria, rising blood levels of urea nitrogen, and even anuria. These renal manifestations are often transitory but may last for several weeks. Reports of these situations are not extensive in the literature but have appeared occasionally in some analyses of clinical series of aneurysmectomies. The important question here is whether the renal dysfunctions observed are the result of the aneurysmectomy per se with its necessary step of occlusion of the aorta for a period of time or whether they appear as a result of the stress in older patients of a major operative procedure irrespective of the aneurysmectomy.

In the following report on dogs, attempt is made to clarify whether distal occlusion of the aorta alone has any direct effect on renal function during the acute phase and also later during the follow-up period. Clearance studies measuring glomerular filtration rate and renal plasma flow were obtained in dogs in which the aorta below the renal vessels was clamped for a period of 2 hours. Estimation of the renal blood flow was also obtained in the acute portion of the experiments by using a modified form of the Baldes and Herrick thermostromuhr placed around one of the renal arteries. Data from these experiments were then compared with the findings that were obtained in a control group of dogs in which the aorta was left intact.

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EXPERIMENTAL METHODS

Female dogs ranging in weight from 11 to 20 kilograms, anesthetized with 35 milligrams of pentothal sodium per kilogram of body weight, were used in both the experimental (aortic occlusion) and control groups. The bladders of these dogs were catheterized to enable collection of urine. About 500 cubic centimeters of sterile normal saline solution were infused intravenously for initial hydration during the first hour. Then, a continuous drip of 1.3 cubic centimeters of normal saline per minute was administered throughout the surgical preparation and during the course of the experiment.

The surgical procedures were carried out as follows: The abdomen was opened under sterile conditions and the region of the right kidney exposed. The renal artery on this side was then separated from all other structures by careful dissection in order not to injure or sever nerve fibers going to the kidney. In order to monitor the blood flow in the right kidney continuously, a modified form of the Baldes and Herrick type thermostromuhr (flowmeter) was placed around the right renal artery, without cutting it or in any way constricting it, at a point between its origin from the aorta and its distal bifurcation. The wire leads were brought out through the abdominal incision for later electrical hookup. Also at this time, a segment of aorta just distal to the renal vessels was exposed to be clamped later for 2 hours with a noncrushing clamp in the experimental group but not in the control animals. All dogs were then maintained on anesthesia and their abdominal incisions approximated but not sutured until after completion of the

TABLE I.—MEAN C_{PAH} AND C_{CREAT} IN DOGS THROUGHOUT EXPERIMENTS

	Initial	*½ hr.*	*2 hrs.*	*2½ hrs.*	*4 hrs.*	*24 hrs.*	*1 week*
	C_{PAH} (C.C. PER MIN.)						
Control							
Mean	150.3	—	163.2	—	107.7	145.4	214.9
S.D. ±	29.6	—	36.8	—	9.3	14.9	46.5
Per cent	100	—	108	—	72	97	143
Experimental*							
Mean	149.1	108.2	112.8	120.3	110.1	159.9	133.7
S.D. ±	23.5	31.1	20.9	36.6	26.3	28.6	24.6
Per cent	100	73	76	81	74	107	90
	C_{CREAT} (C.C. PER MIN.)						
Control							
Mean	65.0	—	73.1	—	64.8	61.5	101.4
S.D. ±	11.1	—	12.8	—	14.7	10.3	32.9
Per cent	100	—	112	—	100	95	156
Experimental*							
Mean	47.0	—	49.9	—	53.5	65.0	40.4
S.D. ±	7.2	—	6.3	—	8.3	6.4	7.4
Per cent	100	—	106	—	114	138	86

Note: Control group=5 dogs; experimental group=9 dogs; %=per cent of initial value.
*In the experimental group only, the aorta was clamped for 2 hours immediately after initial observations were made. The ½ hour and 2 hour observations were made while the clamp was in place whereas the remainder were obtained after its release.

experiment. Renal clearances of creatinine and para-aminohippuric acid (PAH), and blood flow observations were obtained before, during, and after the periods following aortic occlusion in the experimental animals and at comparable times in the control dogs.

Initially, in the infrarenal aortic occlusion dogs, right renal artery blood flow measurements (thermostromuhr) and clearance determinations were obtained. These were again repeated ½ hour and 2 hours after occlusion of the aorta; then again ½ hour and 2 hours after removal of the clamp. In the control group the same data were obtained at the beginning, at 2 hours, and at 4 hours after the start of the experiment. Subsequent to these determinations the thermostromuhr was removed from all dogs, and the abdominal incisions were sutured. Twenty-four hours and 1 week after the day of the experiment, renal clearances were again obtained in all dogs (but no thermostromuhr measurements). The dogs were not anesthetized during these recordings.

Creatinine and PAH clearances were obtained essentially by the method of Selkurt and associates (10). Priming doses of 250 milligrams of creatinine and 50 to 100 milligrams of PAH were initially administered intravenously followed by a maintenance drip of a solution of normal saline containing 0.8 per cent of creatinine and 0.09 per cent of PAH throughout the duration of the experiment. Clearances were obtained by collecting a 15 minute urine sample and obtaining a blood sample halfway during the period of urine collection. The urine and blood samples were then analyzed for creatinine by the alkaline picrate method of Folin and Wu and for PAH by Smith's modification of the method of Bratton and Marshall. The difficulties and limitations inherent with the use of the thermostromuhr were taken into consideration, and changes in the renal blood flow observed from its use were accepted for their qualitative rather than quantitative values, during the period immediately after application and release of the aortic clamp. The systemic arterial pressure was obtained by inserting a catheter into the proximal aorta by way of the carotid artery and hooking it up to a strain gauge.

RESULTS

Nine experiments were performed in dogs in which the aorta distal to the renal vessels was clamped for 2 hours and then released. Clearance studies and observations on the right renal artery blood flow with the thermostromuhr were obtained at intervals throughout the experiments. The clearance

studies were repeated on the following day (about 24 hours later) when the dogs were awake and then again 1 week later. Control experiments were carried out on 5 dogs in which the aorta was not clamped.

Effect on creatinine and PAH clearances of distal occlusion of the aorta. It may be seen from Table I and Figure 1 that the mean C_{CREAT} and C_{PAH} in the control dogs did not change appreciably during the course of the experiments from their initial values except for some rise in both 1 week later. Thus there was a rise in the C_{CREAT} to 156 per cent and in the C_{PAH} to 143 per cent of their initial values. This rise is most likely a reflection of the fact that the latter data were obtained from the dogs when they were awake and suggest a slightly depressed renal function due to anesthesia on the day of the experiments. The effect on the mean C_{CREAT} in the experimental group of animals was similar to that in the control group, although the last determination (1 week) showed a drop to 86 per cent of the initial value. A fall to 76 per cent in the C_{PAH} resulted 2 hours after clamping of the aorta; however, 2 hours after its release the C_{PAH} was the same as in the control dogs (74 per cent vs. 72 per cent). The significance of the differences noted between the control and the experimental clearances is questionable because the range of the calculated standard deviations is wide enough to bring the values close together as shown in Figure 1.

Effect of distal aortic occlusion on the renal blood flow (RBF) calculated from the C_{PAH} and also from observations with the thermostromuhr. The RBF in the two kidneys of the dogs was calculated from hematocrit values and the C_{PAH} since the latter measures renal plasma flow. In Table II the mean values obtained in both the experimental and the control groups are shown. A small reduction in the flow of blood was noted in both groups with the experimental group exhibiting no greater fall at 4 hours than the controls, although 2 hours after occlusion of the aorta, the mean flow was lower than in the controls (76 per cent vs. 114 per cent of the initial values).

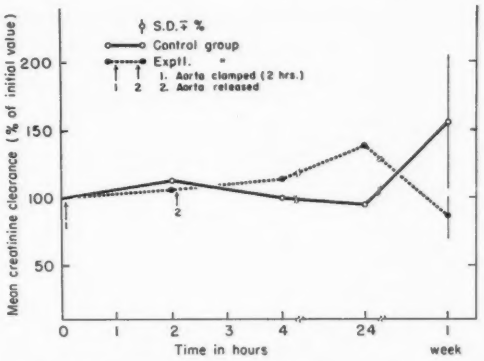

FIG. 1. Effect on creatinine clearance (C_{CREAT}) of aortic occlusion distal to the renal vessels in dogs. S.D., standard deviation.

The latter is more apparent than real because of the wide range in the calculated standard deviations (Fig. 2). Also, the calculated changes in the RBF in essence reflect changes in PAH clearances, although minor variations in hematocrit also affect these values.

It should be pointed out with respect to the flow of blood in the right renal artery as measured with the thermostromuhr that this was only determined during the acute phases of the experiments as the instrument was removed during closure of the abdomen of these dogs; thus no such data were obtained at 24 hours and 1 week. Examination of the mean values (Table II) shows the obvious discrepancy between them and those obtained from the C_{PAH}. The flows by this method are roughly about twice those obtained by calculation from the clearance of PAH. For example, the control mean flow as measured by the flowmeter was 277 cubic centimeters per minute for one kidney (right renal artery) compared with 241 cubic centimeters per minute for both kidneys derived from C_{PAH}. This, of course, is highly inaccurate and is consistent with the limitations in the use and reliability of the thermostromuhr, although still of value for its qualitative rather than quantitative behavior. Thus, comparison of the RBF from the flowmeter with the RBF from the C_{PAH}

TABLE II.—MEAN RENAL BLOOD FLOW (RBF) (FROM C_{PAH} AND STROMUHR) AND MEAN AORTIC PRESSURE IN DOGS THROUGHOUT EXPERIMENTS

	Initial	*½ hr.*	*2 hrs.*	*2½ hrs.*	*4 hrs.*	*24 hrs.*	*1 week*
	RBF ($_{PAH}$) (C.C. PER MIN.)						
Control							
Mean	240.9	—	264.8	—	180.1	208.3	311.0
S.D. ±	57.3	—	54.1	—	14.7	14.1	71.1
Per cent	100	—	114	—	75	86	129
Experimental*							
Mean	239.8	175.8	182.2	197.8	185.7	240.0	193.7
S.D. ±	36.7	48.7	32.7	58.9	46.1	45.9	35.7
Per cent	100	73	76	82	77	100	81
	RBF (STROM.†) (C.C. PER MIN.)						
Control							
Mean	277.2	—	262.8	—	253.5	—	—
S.D. ±	44.2	—	42.5	—	37.7	—	—
Per cent	100	—	95	—	91	—	—
Experimental*							
Mean	196.5	171.5	167.5	168.0	205.1	—	—
S.D. ±	21.9	25.1	18.5	23.6	26.1	—	—
Per cent	100	87	85.2	85.5	104.4	—	—
	AORTIC PRESS. (MM. HG.)						
Control							
Mean	149	—	157	—	154	—	—
Experimental*							
Mean	146	165	167	155	148	—	—

Note: Control group=5 dogs; experimental group=9 dogs; %=per cent of initial value.
*In the experimental group only, the aorta was clamped for 2 hours immediately after initial observations were made. The ½ hour and 2 hour observations were made while the clamp was in place whereas the remainder were obtained after its release.
†The stromuhr measured flow in right renal artery only. (C_{PAH} and C_{CREAT} of course were measured in *both* kidneys.)

show essentially the same percentile alterations in both the control and the experimental groups (Table II and Fig. 2).

Immediate changes in the right renal artery flow during clamping of the distal aorta and also during its release were detected with the thermostromuhr since continuous direct observations were made. This record could not otherwise by obtained from clearance studies because of the necessary lapse of time required for obtaining them. In 5 of the 9 dogs in the experimental group there was a fall (not shown here) in the flow of blood immediately upon clamping of the aorta and also upon its release. This was followed in both instances by prompt recovery within 2 to 3 minutes. The magnitude of the fall was about ¼ to ½ of the value in the steady states. No change was observed in the other 4 dogs.

Arterial blood pressure changes during experiments. Table II also shows the changes in the mean aortic pressures above the renal arteries in all dogs. A slight rise in pressure from 149 to 157 millimeters of mercury was noted in the controls at 2 hours and a slight drop to 154 millimeters of mercury in 4 hours. In the experimental group the pressure rise was somewhat greater, i.e., from 146 to 167 millimeters of mercury at the end of 2 hours of aortic occlusion, but the pressure subsequently fell back to the original level after release of the clamp. It should be pointed out that there was a slight rise of from 5 to 10 millimeters of mercury in pressure immediately following occlusion of the aorta and a somewhat greater fall of from 10 to 20 millimeters of mercury immediately following release. These responses lasted only about 2 to 5 minutes before return to original levels. These pressure responses occurred simultaneously with the immediate changes in the flow measurements obtained with the thermostromuhr.

DISCUSSION

From the foregoing results it appears that in dogs with normal kidneys, glomerular filtration rate and renal plasma flow obtained from the clearance of creatinine and PAH, respectively, are not altered appreciably during the acute phase of distal aortic

occlusion or even as long as a week later. That there was a transitory fall, lasting only a few minutes, in the flow of blood within the kidney immediately during occlusion of the aorta was noted from the thermostromuhr measurements. This was likely due to increased resistance within the kidney parenchyma as the arterial pressure rose; but it was not sustained and therefore did not contribute appreciably to any depression of renal function, as may be seen by comparing the clearance data of the control animals and those in which the distal aorta was occluded for 2 hours.

Our present study disagrees with the suggestion of Powers and his associates and of Nanson and his co-workers that prolonged clamping of the distal aorta results in renal ischemia with subsequent tubular necrosis and thus a depression in the renal functions. Such renal function studies were not carried out by these workers who also suggested that the untoward effects of aortic occlusion could be prevented by denervating the kidneys or using ganglionic blocking agents. No prolonged increase in the renal vascular resistance was noted in our studies and since no significant changes were noted in the renal functions of the control and the experimental groups, denervation of the kidney does not appear to be of much significance here. Haddy demonstrated that by increasing the renal vein pressure instead of the arterial pressure in dogs with nondenervated kidneys an increase in renal vascular resistance took place thereby causing a relative ischemia. This he referred to as "the venous-flow or resistance reflex." Such a mechanism may play a role in some of the clinical cases in which varying degrees of renal dysfunction are noted after distal aortic aneurysmectomy. One may speculate that perhaps during these operations the renal veins are constricted or occluded by packs and other materials for varying periods of time.

Selkurt (9) carried out similar experiments to those of Haddy. He measured renal blood flows directly from the open ends of renal veins; he also obtained

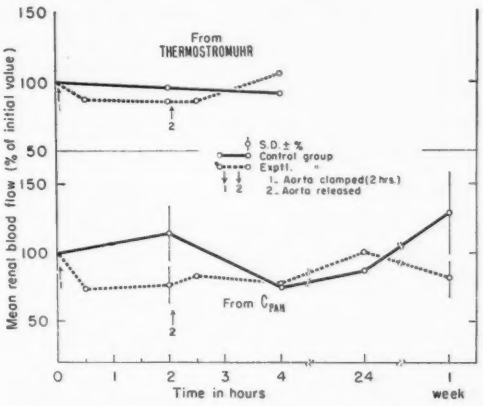

FIG. 2. Effect on renal blood flow (RBF) of aortic occlusion distal to the renal vessels in dogs. S.D., standard deviation; C_{PAH}, p-amino hippuric acid clearance.

creatinine and PAH clearances after graded obstructions of the renal veins. The values in all these measurements and calculations decreased whenever the renal vein pressure was elevated experimentally. The magnitude of the drop in the flow and clearance values was smaller in these experiments which were performed in dogs than in similar experiments carried out in humans by Bradley and his associates (2, 3). These workers demonstrated a greater reduction in effective renal plasma flow and glomerular filtration rate when the renal venous pressure was elevated by abdominal compression with a pneumatic girdle.

Thus it appears clear that, in dogs at least, distal aortic occlusion per se does not contribute to any appreciable renal dysfunction, and it may be speculated that aneurysmectomy of the distal aorta in humans is not fraught with danger simply because it is necessary to occlude the aorta below the renal arteries for a time but may be associated with those dangers incident to any major operative procedure in patients with borderline cardiac and renal function associated with generalized arteriosclerosis. Thurlbeck and Castleman have recently demonstrated that embolization by arteriosclerotic emboli which break off from the aorta when it is clamped during resection

for aneurysms, may lodge into branches of the renal artery in some of these patients and cause varying degrees of renal failure. Such a mechanism probably accounts for most of the difficulties which may result from this type of surgery.

SUMMARY

1. Experiments were carried out in 9 dogs in which the aorta distal to the renal arteries was occluded for 2 hours.

2. Renal function studies such as C_{CREAT} and C_{PAH} and renal blood flow measurements were obtained in these dogs at different intervals before and up to 1 week after such occlusion.

3. No significant depression of renal function or renal blood flow was noted in these animals or in the 5 control dogs whose aorta was not clamped.

4. These findings are at variance with other studies in which it is suggested that distal aortic occlusion results in renal tubular necrosis.

5. The significance of our findings with respect to the effect on the kidneys of resection of aortic aneurysms distal to the renal vessels in humans is discussed in the light of other experimental work.

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SURGICAL TREATMENT OF THE POSTGASTRECTOMY DUMPING SYNDROME

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THE FORMATION of a surgical stoma between the stomach and small intestine, with or without removal of part of the stomach, frequently results in the unpleasant postprandial symptom complex known as the "dumping syndrome." This most commonly occurs immediately after the ingestion of food, particularly high carbohydrate liquids. The patient feels a sensation of dizziness and faintness, even to the point of syncope, and is quickly forced to adopt the reclining position. He usually breaks out in a cold sweat and often notices palpitation and tachycardia. Although the patient may complain of fullness and nausea, vomiting is unusual. An occasional patient will have cramping abdominal distress and diarrhea; however, it is vasomotor symptoms that predominate.

The dumping syndrome occurs more commonly after gastric surgery than was formerly realized. Harvey and associates reported a series of 666 patients who had had a subtotal gastrectomy for duodenal ulcer. One-third of these patients had some degree of the dumping syndrome, the disturbance being persistent in 13 per cent. Reporting on 124 patients who had had a subtotal gastrectomy, Muir found that only 9 were completely free of digestive disturbances postoperatively (excluding stoma ulcers); 90 patients, or 75 per cent, suffered at some time from the dumping syndrome, and of these 15 were unable to resume work for at least 5 months.

Rapid gastric emptying was found in a roentgenographic study of these patients by Mix who in 1922 coined the phrase "dumping syndrome" for this disturbance. Muir found that the symptoms could be reproduced by distending the jejunum with a balloon and concluded that the syndrome was caused by distention of the upper jejunum resulting from precipitate emptying of the gastric remnant. The most convincing evidence favoring the mechanical origin of this disturbance is brought forward by Machella, who studied 20 postgastrectomy patients with this syndrome. He found their symptoms were accompanied by a rise in blood pressure, both systolic and diastolic, and an increase in pulse rate. Hyperglycemia, not hypoglycemia, was encountered during the period of dumping. The symptoms were reproduced by the oral administration of glucose or sucrose, but not by glucose administered intravenously. Ingestion of hypertonic solutions of protein hydrolysates also induced typical symptoms. In normal individuals, the same symptoms were produced by intrajejunal instillation of hypertonic solutions or by distention of the jejunum with a balloon. He concluded that loss of the reservoir function of the stomach permits foods with an abnormally high osmotic pressure to reach the jejunum rapidly, thereby attracting fluid from the intravascular space into the small bowel and producing marked distention. In support of this hypothesis, Roberts, Randall, and Farr demonstrated a decrease in plasma volume after ingestion of hypertonic solutions. This occurred within 10 minutes and reached a maximum in 30 to 40 minutes. A concomitant elevation of hematocrit was also demonstrated. These investigators concluded that the sudden

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drop in circulating blood volume resulted in sympathetic stimulation which emanated from pressoreceptors.

That the reduced plasma volume may be important in the pathogenesis of the dumping syndrome was demonstrated by Jordan and associates (12) who found that the subjective symptoms could be ameliorated by the concomitant administration of blood or plasma volume expanders. It appears that changes in hemodynamics accentuate the blood volume deficit. Hinshaw and coworkers (9) found that symptomatic patients demonstrated a striking increase in peripheral blood flow, and Morris and associates found that these patients also have an increase in renal blood flow.

Many observers have found the dumping syndrome to occur less frequently after the Billroth I type of gastrectomy, with the residual proximal stomach anastomosed to the duodenum. Bohmansson, reporting on an extensive series of patients with the Billroth I reconstruction, found a low incidence of postoperative digestive symptoms. Higginson and Clagett reported 95 cases of Billroth I gastrectomy; the patients had fewer digestive disturbances and were better able to maintain body weight. Likewise, Ross and Meadows noted less "dumping" after Billroth I gastrectomy, but recurrent ulceration was frequent when the procedure was utilized for duodenal ulcer.

Perman reported treating 25 patients with severe dumping syndrome by conversion from a gastrojejunal anastomosis to an end-to-end gastroduodenostomy. All but 4 patients were much improved, with diminution of symptoms and satisfactory weight gain. Hinshaw, Stafford, and Joergenson (10) converted 5 "dumping" patients from Billroth II to Billroth I reconstruction and found not only improvement in symptoms but also objective improvement as measured by a lessened fall in plasma volume and a diminution in peripheral blood flow following a glucose test meal.

However, Moore and Harkins, using the Billroth I anastomosis after rather extensive gastrectomy for duodenal ulcer, found the incidence of the dumping syndrome to be 32.6 per cent. Wallensten and Gothman reported 364 patients upon whom a Billroth I gastrectomy had been performed. Although nutritional difficulties were much less common, they found the incidence of the dumping syndrome to be 10.3 per cent, or the same as that following the Billroth II type of anastomosis. They believe the incidence of the dumping syndrome is not altered by a Billroth I reconstruction but rather is a function of the amount of stomach resected.

A variety of other disturbances and symptom complexes occur with less frequency in the postgastrectomy patient. These have been described in detail by Jordan (11).

An excessive loss of fat and nitrogen in the stools has been reported in patients with the dumping stomach syndrome. This loss of nutriment is less after a gastroduodenal anastomosis than after a gastrojejunal anastomosis. Wollaeger, using a diet containing 200 grams of fat daily, found normal individuals excreted 8.7 grams, patients with Billroth I gastrectomy 12.3 grams, and those with Billroth II gastrectomy 19.9 grams per day. These findings were confirmed by MacLean and co-workers and Everson.

In addition to a diminution in the reservoir function of the stomach after partial gastrectomy, the size of the gastroenteric stoma created has been considered of importance in the pathogenesis of the dumping syndrome. Porter and Claman and Abbot, Krieger, and Levey reported cases of this disorder treated by narrowing the gastrojejunal stoma with improvement in symptoms. Dragstedt, and Zollinger and Krieger and their associates have found a lessened incidence of the dumping syndrome when small gastrojejunal stomas are utilized at the initial operation. In the usual Billroth I gastrectomy, the diameter of the duodenum limits the size of the surgical stoma, which is

considerably less than the usual gastrojejunostomy. Roentgenologic studies by many observers have disclosed much slower emptying of the gastric remnant with the Billroth I gastrectomy.

The present study is an outgrowth of a survey (6) conducted of patients operated upon for gastroduodenal lesions during the period from 1947 to 1954. The cases of 1,366 patients receiving definitive gastric surgery were reviewed in a gastrointestinal follow-up clinic. During the course of the study, 21 patients severely disabled by the dumping syndrome failed to respond adequately to a dietary regimen and it was decided to undertake revisional surgery. In those patients in whom the residual stomach provided an adequate reservoir, it was the objective of the secondary operative procedure to narrow the stoma either through (1) conversion to a Billroth I gastroduodenostomy, (2) takedown of gastrojejunostomy with pyloroplasty, or (3) direct plastic narrowing.

In patients in whom the residual stomach was inadequate in size or absent, an attempt was made to restore the reservoir function of the stomach by the interposition of a jejunal pouch. This is a modification of the procedure advocated by Longmire and Beal for reconstruction following total gastrectomy. Three loops of jejunum are plicated together in such a fashion that a common lumen is created, as described by Hays. The steps in this procedure are presented diagrammatically in Figures 1 through 5.

After the correctional operations, the patients were again studied at 6 month intervals in the gastrointestinal follow-up clinic. Continuing records of body weight were maintained on all patients. Each patient was interviewed independently by two observers during each clinic visit. The clinical result obtained in each case was determined according to the following criteria.

Excellent: Patient completely free of gastrointestinal complaints, maintaining normal body weight, and continuing usual vocational and social activities.

Good: Patient completely free of ulcer symptoms but having mild gastrointestinal complaints controlled completely by simple dietary means.

Fair: Patient free of ulcer symptoms but with gastrointestinal complaints controlled incompletely by diet or simple medication, but not interfering with normal activities.

Poor: Patient free of ulcer disease but incapacitated to a significant degree by gastrointestinal symptoms or malnutrition.

Failure: Patient with presumptive or conclusive evidence of recurrent peptic ulceration.

Eighteen of the patients in the present series were men and 3 were women; their ages varied from 22 to 63 years. Seventeen patients had had duodenal ulcer prior to the initial operation, 2 had had benign gastric ulcer, and 2 carcinoma of the stomach. All patients have been available for follow-up examination on at least 3 separate occasions. The minimum period of time elapsing between revisional surgery and the last evaluation was 1½ years, the maximum 5½ years.

The procedures which were used were as follows: (1) conversion to Billroth I, 11 cases; (2) de-gastroenterostomy, 4 cases, with pyloroplasty in 2 and with gastric resection in 2; (3) plastic narrowing of gastroduodenostomy, 1 case; (4) interposition of jejunal pouch, 5 cases, after total gastrectomy in 2 and after subtotal gastrectomy in 3 cases.

RESULTS

All patients had suffered extensive weight loss after the initial gastric surgery; this averaged 25 per cent over the previous normal body weight. Weight gain after correctional surgery occurred in these 21 patients as follows: none in 2 cases, less than 10 per cent in 8, 10 to 20 per cent in 8, 20 to 30 per cent in 2, and more than 30 per cent in 1. Thus only 2 of the patients failed to gain weight. In 9 of the 21 patients weight returned to normal. Calculations have all been based on the "normal standard" for

TABLE I.—PATIENTS CONVERTED FROM BILLROTH II TO BILLROTH I

Case No.	Age	Sex	Lesion	Weight			Follow-up, months	Result
				Normal	Preop.	Present		
1	60	M	DU	198	125	160	31	Excellent
2	54	M	GU	148	107	126	60	Excellent
3	44	M	DU	155	128	146	39	Excellent
4	39	M	DU	190	131	175	43	Excellent
5	22	M	DU	140	115	127	42	Excellent
6	42	M	DU	190	130	181	45	Good
7	36	F	DU	160	135	160	49	Good
8	44	F	DU	110	79	94	29	Good
9	40	M	DU	150	132	132	21	Fair
10	36	M	DU	170	133	138	20	Fair
11	32	F	DU	150	96	80	62	Poor

each patient, in relation to height. The average weight gain in the entire group was 17 pounds.

The clinical results in the 21 patients as established by the criteria outlined are as follows: excellent 8, good 5, fair 5, poor 2, and failure 1.

The largest group of patients were those who had had partial gastric resection and were treated by conversion from a gastrojejunal to gastroduodenal reconstruction. In every patient the gastrojejunal stoma measured 4 to 6 centimeters in diameter. After completion of the revisional operation the gastroduodenal stoma was estimated to be 1 to 1.2 centimeters in diameter. In 1 patient an unexpected marginal ulcer was found. This called our attention to the fact that these patients were being subjected to an increased hazard of recurrent peptic ulceration. Therefore, in the last 3 patients an incidental vagotomy was performed at the time of secondary surgery. There have been no recurrent ulcers in any of the 11 patients, although in 2 the postoperative period has been more than 5 years.

The results in the 11 patients treated by conversion from Billroth II to Billroth I are summarized in Table I. Five patients have obtained an excellent result and are completely asymptomatic. Three additional patients are classed as good, indicating only minor symptoms. Therefore, the results in 8 of the 11 patients have proved to be clinically satisfactory for the operative treatment of the dumping syndrome. Two patients are considered to have a fair result and 1 patient is unimproved. There has been a close correlation between gain in body weight and the clinical result obtained. The patients who have had the most striking symptomatic relief have for the first time since gastric resection been able to eat an adequate diet. As a result of the sharp increase in caloric intake, these patients have, in general, exhibited significant weight gain in the immediate postoperative period and this has been maintained throughout the follow-up period. In 1 patient a nutritional balance study was performed and a sharp increase in the efficiency of fat absorption was demonstrated after conversion to Billroth I gastroduodenostomy, as described previously (27). On the usual daily intake of fat in the diet, however, this improved absorption would account for only about 25 additional calories per day. Therefore, it seems much more likely that the weight gain is due almost entirely to quantitatively increased caloric intake. The patients with satisfactory results have been able to eat unselected diets including high carbohydrate liquids. All have shown progressive improvement in physical stamina and energy as a corollary to their improved nutrition. All patients with satisfactory results have returned to their previous occupations and are able to carry a full work load without difficulty.

Two patients had had duodenal ulcer treated by vagotomy and gastroenterostomy. In order to conserve to the maximum the reservoir function of the stomach, these patients were treated by take-down of the gastrojejunostomy and Heineke-Mikulicz pyloroplasty. In both patients preoperative gastric secretory studies had disclosed complete vagotomy. Neither patient has had a satisfactory clinical result, although the "dumping" symptoms completely disappeared. Both had gastric retention to a troublesome degree. Nine months after the revisional operation, a large benign gastric ulcer developed in 1 patient (Case 12) and this case therefore is classed as a failure. The patient was operated upon a third time and

a conservative Billroth I gastric resection performed (antrectomy or hemigastrectomy). The patient has now been completely asymptomatic for 5 years. The second patient is still having periods of gastric retention and diarrhea 3½ years postoperatively.

In 2 men in the older age group, an obstructing duodenal ulcer had been treated by gastroenterostomy. Both patients had marginal ulcer in addition to severe dumping. The patients were both treated by vagotomy, degastroenterostomy, and conservative gastric resection with Billroth I reconstruction. The clinical results have been good and excellent respectively both as regards the dumping symptoms and the peptic ulcer symptoms. These results are summarized in Table II.

In Case 16 (Table II), a duodenal ulcer had been treated by vagotomy and hemigastrectomy with a Billroth I reconstruction. Despite the seemingly optimal situation, the patient undeniably had severe dumping and had lost weight from 175 to 106 pounds. At reoperation, the gastroduodenostomy stoma was found to admit 4 fingers readily and had apparently been made by using the Finney-von Haberer modification. The anterior portion of the anastomotic line was reopened and then sutured longitudinally resulting in sharp narrowing of the anastomotic channel. At the conclusion of this plastic procedure, the stoma would admit only the index finger. The patient made a dramatic postoperative recovery, and within 6 months had gained 54 pounds. He still gets occasional mild dumping but this does not interefere with a full work schedule and an otherwise normal life.

In the remaining 5 patients (Table III), the gastric reservoir was either markedly deficient in size or completely absent. In 3 patients radical subtotal gastrectomy had been performed for duodenal ulcer. It was believed that conversion of these patients to a Billroth I operation would probably not afford relief from the dumping symptoms.

TABLE II.—PATIENTS TREATED BY DEGASTROENTEROSTOMY OR PLASTIC PROCEDURE

Case No.	*First operation*	*Second operation*	*Weight gain*	*Result*	*Follow-up, months*
12	Vag., GE	De-GE, pyloroplasty	+11	Failure	60
13	Vag., GE	De-GE, pyloroplasty	+8	Fair	42
14	GE	Vag., De-GE, Bil. I	+18	Excellent	46
15	GE	Vag., De-GE, Bil. I	+12	Good	39
16	Vag., Bil. I	Plastic narrowing	+54	Good	63

TABLE III.—PATIENTS TREATED BY JEJUNAL POUCH INTERPOSITION

Case No.	*Age*	*Sex*	*Lesion*	*Weight*			*Follow-up, months*	*Result*
				Normal	*Preop.*	*Present*		
17	55	M	DU	125	91	106	16	Poor
18	59	M	DU	158	124	160	66	Excellent
19	22	M	DU	142	121	128	30	Excellent
20	37	M	Ca	150	115	123	42	Fair
21	53	M	Ca	149	118	129	52	Fair

Therefore, a 3 loop jejunal pouch was interposed between the gastric stump and the duodenum, as outlined in Figures 1 through 5. Two patients have had highly successful clinical results and are now able to eat meals of normal size and composition without subjective symptoms. Both consider themselves entirely symptom-free. The third patient was lost to follow-up after 16 months. At that time, although he had gained 15 pounds in weight, he complained that his subjective symptoms were unimproved and his case is, therefore, classed as a poor result.

The final 2 patients both had total gastrectomy for carcinoma of the stomach, 7 and 9 years previously, respectively. Although there was no evidence of recurrence of the cancer in either patient, both were totally disabled by dumping symptoms accompanied by intractable diarrhea. In these patients, therefore, the 3 loop jejunal pouch was interposed between esophagus and duodenum. Both patients have shown moderate improvement postoperatively but still must be considered gastric cripples and the results are classed as fair. Each patient has shown a modest weight gain, can eat more food at each meal, and has less severe

diarrhea than before. Both patients, however, still have the subjective symptoms of dumping, although these are less frequent and less severe than preoperatively. Thus, only 2 of the 5 patients have satisfactory clinical results; this seems a worthwhile salvage rate in patients so severely disabled.

DISCUSSION

Intensive research during the past 20 years has established that the disordered function in the postgastrectomy dumping syndrome results from the rapid passage of hyperosmolar materials into the upper small intestine. This results in sudden distention of the duodenum or jejunum which initiates a "stretch reflex." The symptoms provoked are largely vasomotor and can be reproduced in normal volunteers by the sudden inflation of a balloon within the lumen of the small bowel. The volume of these materials is rapidly increased by the attraction of fluid from the intravascular space across the intestinal membrane into the lumen. This reaction further reinforces the local distention.

The rapid osmotic attraction of intravascular fluid into the small intestine results in a sudden drop in plasma volume. The resultant blood volume deficit is not in the range encountered in hemorrhagic shock, but none the less could conceivably enhance the vasomotor effects produced by intestinal distention. That this factor is significant in the dumping syndrome is demonstrated by amelioration of the characteristic symptoms by concomitant intravascular replacement therapy. Apparently the intestinal stretch reflex sensitizes pressor receptors so that a drop in plasma volume of 500 to 700 cubic centimeters is adequate to activate the reflex effects. The tachycardia, hypotension, and perspiration can be explained on this basis, and the weakness, dizziness, and faintness are presumably due to diminished cerebral blood flow. The increased cutaneous and renal blood flow is not easily explained but certainly could produce a maldistribution of the already deficient blood volume, enhancing the shocklike picture.

The anatomic defect common to all patients with the dumping syndrome is the ablation or bypass of the pylorus, with the surgical creation of a relatively large sphincterless stoma into the small intestine. This permits the rapid, uncontrolled passage of ingested food and fluids into duodenum or jejunum. A secondary factor of considerable importance is the degree of encroachment on the storage function of the stomach. The less gastric reservoir remaining, the more rapid will be the emptying into the small intestine until after total gastrectomy the incidence of the dumping syndrome approaches 100 per cent.

In the present study, 21 patients with intractable dumping syndrome were subjected to revisional surgery in an attempt to correct one or both of the defects created by the original surgical therapy. In 11 patients who had an adequate residual stump, conversion from a Billroth II gastrojejunostomy to a Billroth I end-to-end gastroduodenostomy produced a satisfactory clinical result in 8. There is no evidence available to indicate that the duodenum is any more resistant to "dumping" than is the jejunum. It is believed that the significant factor in the success of this procedure is the end-to-end anastomosis between stomach and duodenum. The diameter of this stoma is limited by the diameter of the duodenum. After the traditional two layer infolding anastomosis, the internal diameter is distinctly less than that of the duodenum. Although this is still larger than the normal intact pylorus, there is, nevertheless, a demonstrable delay in emptying of the gastric stump as established by both roentgenographic and dye dilution techniques. The increased efficiency of fat absorption after gastroduodenostomy is considered desirable but relatively unimportant. The significant weight gain shown by most such patients is the result of the increased volume of food ingested which in turn results from the absence of dumping symptoms.

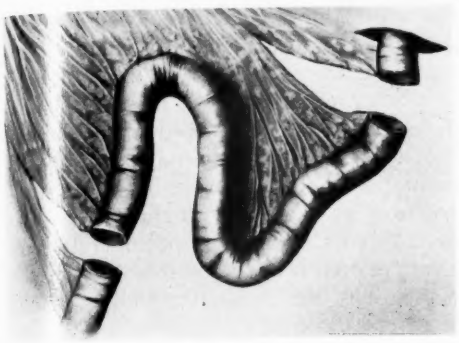

FIG. 1.

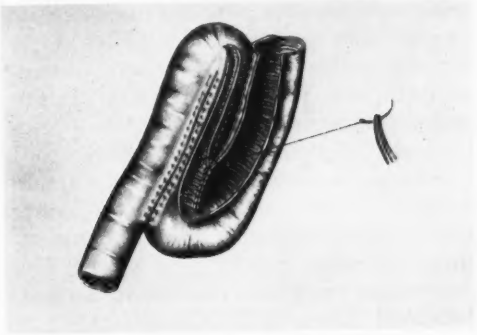

FIG. 3.

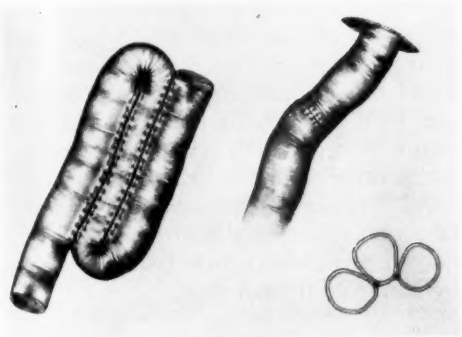

FIG. 2.

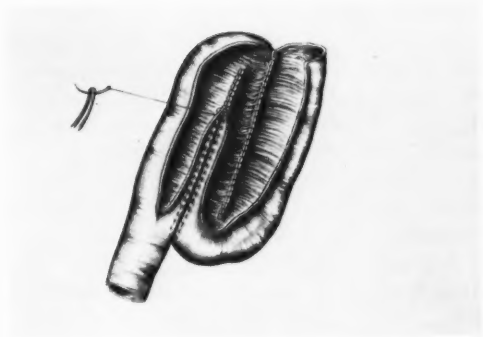

FIG. 4.

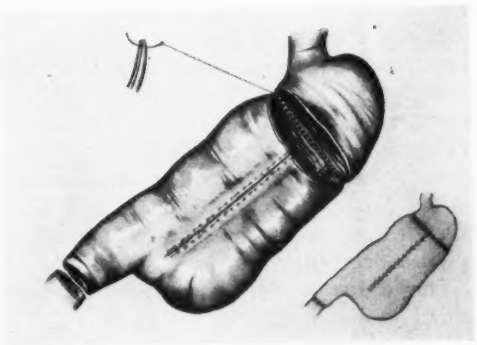

FIG. 5.

In the 4 patients with "dumping" following gastroenterostomy, resection of the gastric antrum with a Billroth I reconstruction seemed to be more effective than simple take-down of the gastrojejunostomy and Heineke-Mikulicz pyloroplasty. However, the 2 patients in each group constitute much too small a number to justify such a conclusion. The 2 patients treated by pyloroplasty had had physiologically complete vagotomy as part of their primary procedure. This procedure undoubtedly enhanced the gastric retention observed in both patients and was also unquestionably related to the development of benign gastric ulcer in 1. In the 2 patients in whom gastroenterostomy alone had been used in the treatment of obstructing duodenal ulcer, marginal ulceration was present in addition to intractable dumping. The combination procedure of vagotomy and Billroth I antrectomy was highly effective in correcting both disturbances in these 2 patients.

The case of the patient with severe dumping following vagotomy and Billroth I

hemigastrectomy is most instructive, since the revisional operation did not alter in any way the routing of the gastrointestinal tract nor did it alter the gastric reservoir. In this patient plastic narrowing of the gastroduodenal anastomosis from 4 finger to 1 finger size was sufficient to produce almost complete disappearance of the subjective features of the dumping syndrome and resultant extensive gain in body weight. This observation reinforces the conclusion that the small stoma is the important factor rather than the exact level of the upper small intestine which is anastomosed to the residual stomach.

There were 5 patients, 3 with subtotal and 2 with total gastrectomy, in whom an effort was made to reconstitute a reservoir by the construction of a 3 loop jejunal pouch. This was interposed between gastric stump or esophagus and duodenum. Here again, an effort was made to achieve outlet control by end-to-end anastomosis between interposed jejunum and duodenum. Although all 5 patients showed some improvement, only 2 results can be considered satisfactory clinically. There was, at first, considerable stasis of ingested food, but the jejunal stomach seemed to function fairly adequately in these patients within 1 to 2 weeks. Since this was by all odds the most severely handicapped group in the study it is not surprising that the results obtained by revisional surgery were less desirable than those achieved in the other patients reported. None the less, the stakes seem high enough that further efforts at gastric reservoir replacement seem justifiable.

The data in the researches reviewed added to the results in the present study indicate that preventive measures could be utilized to advantage in the performance of gastric surgery toward the end of preventing or minimizing the dumping syndrome. Certainly the frequent occurrence of this disturbance with its high morbidity militates against the free use of surgical therapy in such a common benign lesion as peptic ulcer. First and foremost, it seems apparent that gastrointestinal stomas of small size, i.e., distinctly less than the diameter of the small intestine at that level, will be followed by a lower incidence and a lessened severity of "dumping." It has been observed that small gastrointestinal anastomoses cause less angulation and distortion during reconstruction and actually seem to function more rapidly during the postoperative recovery period. It is further apparent that the incidence of the dumping syndrome bears an inverse ratio to the amount of stomach remaining after operation. It would seem eminently worthwhile to conserve gastric tissue to the maximum extent compatible with a surgical procedure soundly conceived for the primary disease present. Severe disability due to dumping occurs so regularly after total gastrectomy that when this procedure is required an immediate jejunal interposition could be considered worthwhile. With the extensive exposure required for an adequate total gastrectomy, such a method of reconstruction requires surprisingly little additional time.

SUMMARY AND CONCLUSIONS

The recent literature is surveyed to indicate that the disordered function in the dumping syndrome results from the rapid passage of hyperosmolar materials into the upper intestine. This produces an intestinal stretch reflex which is further enhanced by the sudden influx of fluid osmotically attracted from the intravascular space. The drop in plasma volume is sufficient to trigger pressor receptors, further emulating a shocklike picture. The anatomic defect common to all "dumping" patients is a relatively large sphincterless stoma into the small intestine. Rapid egress of ingested foods is accelerated to the extent that the gastric reservoir has been diminished.

Twenty-one patients with medically intractable dumping syndrome were treated by revisional surgery with an attempt to correct one or both of these surgically created defects. Eleven patients were converted from Billroth II to Billroth I reconstruction

with a clinically satisfactory result in 8. Weight gain correlated well with amelioration of symptoms. The small diameter of the gastroduodenal stoma is considered to be the most important factor.

In 4 patients with dumping after gastroenterostomy, Billroth I hemigastrectomy seemed to be the most effective therapy. One patient with vagotomy-hemigastrectomy was effectively treated by plastic narrowing of the gastroduodenostomy.

A gastric reservoir was reconstructed in 5 patients by using a 3 loop jejunal pouch interposed between gastric stump or esophagus and duodenum. In this severely disabled group a satisfactory result was achieved in only 2.

Preventive measures against development of the dumping syndrome after gastric surgery are urged, with the creation of gastrointestinal stomas of small size and the preservation insofar as possible of gastric reservoir capacity.

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EXPERIMENTAL CLOSURE OF THE DUODENAL STUMP WITH A PERITONEAL GRAFT

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IN MOST CASES the surgeon performing a subtotal gastrectomy with creation of a gastrojejunostomy is able to obtain a secure closure of the duodenal stump without undue difficulty. Occasionally, however, when a duodenal ulcer is present, the management of the stump poses a real problem. If a satisfactory closure proves impossible after the surgeon is committed to a gastrectomy, some substitute measure such as catheter drainage of the stump becomes necessary.

The current investigation was undertaken to study a method for handling the open duodenal stump by the use of a free autogenous parietal peritoneal graft.

MATERIALS AND METHODS

Adult mongrel dogs of both sexes fasted for 24 hours were used as experimental animals. Intravenous veterinary pentobarbital sodium was used for anesthesia and a slow infusion of isotonic sodium chloride solution continued throughout the operation. Using sterile technique the abdomen was entered through a vertical midline or left rectus muscle splitting incision. In all animals a resection of approximately 60 per cent of the distal portion of the stomach was carried out with the duodenum divided just beyond the pylorus. Gastrointestinal continuity was restored by creating a gastrojejunostomy of the Hofmeister type. In a control group of 5 animals the duodenum was left wide open at the time the peritoneal cavity was closed. In the 13 experimental animals the parietal peritoneum was dissected free from the overlying abdominal musculature along one edge of the abdominal incision. Dissection was continued until a piece of peritoneum large enough to cover the open duodenum was obtained.

Since the parietal peritoneum is intimately adherent to the posterior rectus sheath in the upper part of the dog's abdomen, the graft was a composite one of these two layers in most instances. The free graft was sutured over the open end of the duodenum, with the smooth peritoneal surface facing out, by using interrupted sutures of No. 5-0 silk placed through the graft and the duodenal wall at a distance from the cut edge of bowel. Enough sutures were used to provide a watertight closure but care was taken to prevent constriction of the lumen. Rather the graft was placed to cover but not distort the open end of the duodenum. After abdominal wall closure each animal received 600,000 units of aqueous penicillin and 0.5 gram of streptomycin intramuscularly. In each surviving dog this injection of penicillin and streptomycin was repeated daily for 3 days. During the postoperative period, the animals were kept without oral intake for 3 days, receiving a daily intravenous infusion of isotonic sodium chloride and 5 per cent dextrose in water. They were then given liquids by mouth and advanced in the next few days to regular rations.

All dogs which died were studied by postmortem abdominal examination. The remaining 5 animals were observed for periods varying from 28 to 87 days before they were sacrificed and abdominal exploration was carried out. Three of these animals were subjected to laparotomy 48 hours before sacrifice and 62, 84, and 85 days respectively after the initial operation. At this secondary operation the duodenum immediately proxi-

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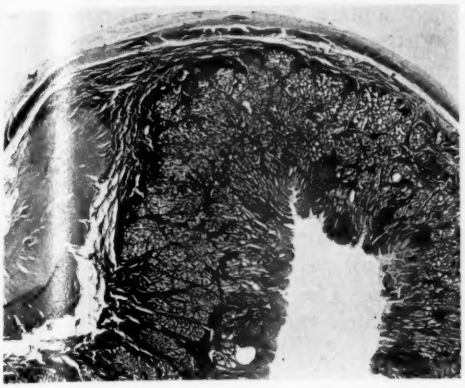

FIG. 1.

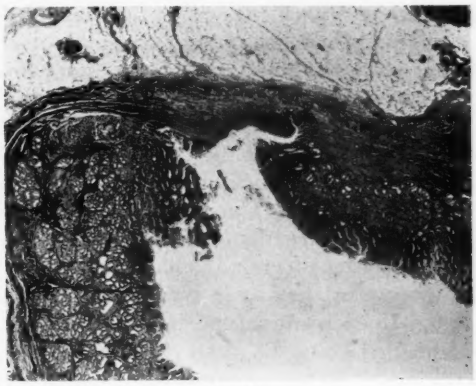

FIG. 2.

FIG. 1. Photomicrograph showing margin between duodenum (left) and graft. The inner surface of the graft has been covered by duodenal mucosa, but muscularis stops at the end of the bowel wall.

FIG. 2. Photomicrograph showing an intact graft without complete lining by duodenal muccsa. There was a chronic inflammatory cellular reaction in this particular area. Grossly, a strong satisfactory closure was present.

mal to the gastrojejunostomy was obstructed completely by tying an umbilical tape around the bowel.

RESULTS

The 5 control animals with open duodenal stumps all died within 48 hours of operation, only 1 dog surviving beyond 24 hours. In all animals there was diffuse chemical peritonitis with bile and serosanguineous fluid pouring from the open end of the bowel. The gastrojejunostomy was intact in each animal.

Two of the 13 animals in the grafted group died on the third postoperative day of causes unrelated to the duodenal stump, one from wound evisceration and the other from aspiration pneumonia. In both animals the graft was intact and without evidence of necrosis at the time of autopsy. In the remaining 11 dogs, evaluation of the graft closure was possible.

All long term survivors ate normally and maintained weight during the period of study. There were no undesirable side effects in the abdominal incision itself after removal of the graft.

Five dogs died from direct failure of the graft to maintain closure of the duodenum. Three of these animals died within the first 24 hours. In 2 of them, the parietal peritoneum was very thin when dissected free from the fused posterior rectus sheath, and the resulting graft proved difficult to suture successfully. In both, at autopsy the point of leak was along the graft suture line. The third death during the first postoperative day occurred in an animal which was allowed to reach too light a plane of anesthesia during the operation. This dog swallowed a large amount of air before anesthetic control was regained so that the stomach and duodenum were quite distended when the abdomen was closed. Again leakage occurred along the suture line of the graft. A fourth dog did well until it died abruptly on the third postoperative day. A hole was found in the center of the graft with a group of round worms projecting through it along with bile-stained fluid. The fifth dog progressed well until its sudden death on the fifteenth postoperative day. A complete disruption of the central portion of the graft was found with a spreading peritonitis.

In the remaining 6 dogs, the graft was well healed without signs of peritonitis when the stump was examined at operation or autopsy. In each instance the graft was intact and

could be readily identified. Adhesions around the stump and attachment to adjacent organs were not responsible for maintenance of the closure in any case. One animal died 18 days postoperatively from obstruction of the efferent limb of the gastrojejunostomy. Despite this obstruction the grafted stump was well healed. The 3 dogs subjected to duodenal obstruction by occlusion with an umbilical tape were all found to have intact grafts when they were sacrificed 48 hours later. In each animal the duodenal loop was distended, but the graft retained normal color and texture. In 2 of these dogs there was gangrene and actual or impending perforation in the wall of the duodenum along its antimesenteric border at a site well removed from the stump closure. The final pair of dogs with successful grafts were sacrificed 1 and 2 months postoperatively without a secondary operation. Satisfactory stumps with intact grafts were found in both of these animals.

Microscopic examination of the grafted segments in these 6 animals showed that the graft remained intact and that the duodenal closure did not result from inversion of the bowel wall. In some of the animals a normal appearing duodenal mucosa had grown across the inner surface of the graft (Fig. 1). In others, the mucous membrane was incomplete and an infiltration of chronic inflammatory cells was present as illustrated in Figure 2.

DISCUSSION

The experiment was designed to provide a severe test for the graft closure. A deliberate effort was made to see that the duodenal stump was kept wide open and without constriction; the graft served merely to cover the unclosed bowel. With this technique graft failure occurred in 5 animals. In 3 of these, a technical error was at least partially responsible for the animal's death. Too thin a graft, the result of dissecting peritoneum away from the fused posterior sheath, was a problem twice; marked distention of the stomach and duodenum coincident with too light a plane of anesthesia occurred once. A fourth animal was discovered at postmortem examination to have a group of round worms projecting through a hole in a graft otherwise intact. The final animal demonstrated a complete graft failure with autolysis of its entire central portion occurring 2 weeks after operation.

The remaining 6 dogs with grafts made satisfactory recoveries and peritonitis did not develop. The percentage of good results might have been increased if the graft had been placed with a continuous suture or if the stump had been partially closed before application of the peritoneal patch. Interrupted sutures were used because it was believed that a continuous suture might narrow the end of the stump rather than leave the duodenum wide open. The leakage resulting in death of several of the animals occurred not through the graft itself but between sutures at the margins of the graft. If a peritoneal graft were applied to a dangerous stump in a patient, the probability of success would be enhanced by closing the bowel as efficiently as possible before application of the graft and by using a meticulous technique in suturing the graft in place. The experiments in which deliberate obstruction of the loop was produced at a later date offer evidence that a graft, if initially successful, can be relied upon to afford satisfactory closure even when there is increased intraluminal pressure.

The use of free grafts to protect anastomoses in the alimentary canal has been explored by other investigators. Free grafts of parietal peritoneum have been used successfully surrounding colon anastomoses in dogs by Devine and by Chester and his associates. Satisfactory results experimentally with these grafts in stomach, small bowel, and colon were reported by Taubenfligel, Wajda, and Senyk. In a similar fashion, experimental esophageal anastomoses have been protected by grafts of pericardium with external nylon mesh support as performed by Moore and Bounous or without additional external support as performed by Adler. Free grafts of

parietal pleura used by McSwain and associates or of visceral pleura used by Deaton and Bradshaw have also proved effective in allowing experimental esophageal anastomoses to heal even when anastomotic technique has been deliberately faulty. On the other hand, in a series of investigations Kleinsasser, Cramer, and Warshaw concluded that although parietal peritoneal grafts provided greater bursting strength when sutured around a careful esophageal anastomosis, this protection could be demonstrated only during the first 5 days after operation. The control anastomoses without grafts proved equally efficient after that time interval.

The problem presented by a duodenal stump covered with a graft is somewhat different from that encountered with an anastomosis surrounded by one. The most severe test of any grafting technique occurs in the early postoperative period when the duodenal stump is under pressure from the quantities of bile and pancreatic and intestinal juices entering this portion of the intestine. Moore and Singleton and McCorkle have reported successful management of the stump with peritoneal grafts. McCorkle performed a loose closure of the duodenum before applying the graft, but Moore and Singleton's experiment paralleled our own in keeping the end of the duodenum open. Taubenfligel and his colleagues reported that Kieturakis had successfully used free peritoneal grafts over the duodenal stump in humans. Hardin, Su, and Battersby employed plugs of omentum to close the duodenum. They found that these grafts failed unless the omental graft was of the pedicle type with intact blood supply. Such a pedicle could act as a site for later obstruction from twisting of the bowel around it. Closure of the stump around a catheter might also be complicated by this type of obstruction, and a persistent duodenal fistula is also possible. A free graft would appear to provide a safer closure in these respects.

On the basis of our own investigations and of those reviewed here, we believe that free peritoneal grafts have a place in the management of the difficult duodenal stump. These grafts are readily available, and the donor site does not produce a weakness in the abdominal wall. Primary efforts should be devoted, of course, to closing the stump as adequately as possible. Reinforcing this closure with a free peritoneal graft affords an additional element of protection. In these cases it is imperative to provide adequate gastric decompression postoperatively either through a nasogastric tube or a gastrostomy. With careful attention to the details of operative and postoperative management it should be possible to minimize complications resulting from the closed duodenal stump.

SUMMARY AND CONCLUSIONS

Subtotal gastrectomy with reconstruction by gastrojejunostomy was carried out in dogs. The use of parietal peritoneum as a free graft to facilitate closure of the open duodenal stump was evaluated. Control animals with open stumps all died in the first 48 hours. Grafts provided satisfactory stump closure in some, but not all, dogs in the experimental group. Technical factors leading to graft failure are discussed. With proper precautions, the use of free peritoneal grafts appears to offer a satisfactory method for dealing with the difficult duodenal stump occasionally encountered in peptic ulcer surgery.

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THE RATE OF HEPATIC BLOOD FLOW IN NORMAL SUBJECTS AND IN PATIENTS WITH PORTAL HYPERTENSION

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THE MEASUREMENT of the rate of hepatic perfusion is a highly desirable complement to investigations of the hemodynamics of the portal circulation. Estimations of hepatic blood flow in human beings, however, have been limited by the lack of suitable techniques. With the application of cardiac catheterization to obtain samples of hepatic vein blood, studies of hepatic blood flow were greatly advanced by Bradley, Ingelfinger, Bradley, and Curry, by Myers, and by Sherlock, Bearn, Billing, and Paterson.

A somewhat simpler method, not requiring the use of cardiac catheterization, was reported in 1952 and 1953 by Dobson and Jones and by Dobson, Warner, Finney, and Johnston. This method was based on the determination of the rate of disappearance from the systemic circulation of an intravenously injected radioactively labelled colloid. The phagocytes of the liver and the spleen were assumed to be responsible for the disappearance of the colloid. The possibility of estimating hepatic blood flow by such a method had already been suggested by the experimental work of Sheppard, Jordan, and Hahn in 1951. In the method developed by Dobson and collaborators, colloidal chromium phosphate labelled with P^{32} was injected into a superficial vein and the rate of removal established in a series of peripheral blood samples.

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In an effort to overcome the intricacies of the preparation of a chromium phosphate colloid of suitable particle size, Vetter, Falkner, and Neumayr, in 1954, reported a modification of the method in which the more readily available colloidal radioactive gold (Au^{198}) was used. In addition, they further endeavored to simplify the procedure by using external countings of radioactivity in peripheral vessels instead of countings in multiple blood samples.

Benacerraf, Biozzi, Halpern, Stiffel, and Mouton, in 1957, reported on another adaptation of Dobson's method. Based on their previous observations that the cells of the reticuloendothelial system phagocytize the complexes of globulin and albumin isolated from heated serum, they used the clearance of a heat-denatured complex of human serum albumin labelled with I^{131} to estimate the rate of hepatic blood flow.

Other methods have been devised and used. Storaasli, Reichman, Gorlin, and Davis, in 1956, and Davis, Batson, Reichman, Gorlin, and Storaasli, in 1958, described the use of an indicator dilution technique. In their method the rate of dilution of an intrasplenically injected bolus of I^{131} labelled serum albumin was recorded from a scintillation probe located over the liver. More recently Reemtsma, Hottinger, DeGraff, and Creech, studied the disappearance rates and extraction ratios of indocyanine green as a new method to estimate hepatic blood flow. Kampine, Stekiel, and Smith, on the other hand, observed decreased clearance rates of this dye in pa-

tients with abnormal hepatic function tests, a factor which may limit the use of the single injection method of estimating hepatic blood flow in patients with altered liver function.

Among these presently available methods Dobson's colloid clearance technique, although perhaps not an entirely unobjectionable method of estimating hepatic blood flow, may nevertheless offer a practical solution in terms of relative simplicity and reasonable accuracy. Its use should make possible the determination of hepatic blood flow in large numbers of patients and normal subjects. When colloidal aggregates of heat-denatured human serum albumin are utilized, their breakdown after phagocytosis is apparently rapid and complete. Furthermore, as no sensitivity reactions have been observed, it is possible that repeated determinations on the same patient may be made without undue risk.

This article is a report on the results obtained in the estimation of hepatic blood flow by the clearance of colloidal aggregates of heat-denatured human serum albumin labelled with I^{131} in a relatively large group of normal subjects and patients with portal hypertension. This report is part of a comprehensive study of the normal and pathologic physiology of the portal circulation being conducted in this clinic.

MATERIALS AND METHODS

Hepatic blood flow was estimated in 1 or more instances in 71 patients. The values of hepatic blood flow in these patients in relation to other variables in the portal circulation are reported in a separate article (14). Twenty-one normal subjects in this group and 4 patients initially suspected of having portal hypertension but in whom liver function studies, splenic portograms, and portal manometrics did not show abnormalities were used as controls of normal hepatic blood flow. The remaining 46 patients had varying degrees of portal hypertension and collateralization of the portal system. Of these, 43 had cirrhosis of the liver; one, metastatic carcinomatous involvement of the liver; another, reticulum cell sarcoma; and the final patient, generalized Hodgkin's disease. In all of the patients in the group that showed abnormalities of the portal circulation, complete splenoportographic and manometric studies of the portal system were made. Of 12 patients who were studied after a surgical portacaval shunt was established, 5 had preoperative determinations of hepatic blood flow while the other 7, in whom this operation had been performed from 5 months to 5 years previously, did not have these preoperative determinations.

Colloidal aggregates of heat-denatured human serum albumin labelled with I^{131} (I^{131} albumin complex) prepared by the method described by Benacerraf and associates were used in the determination of hepatic blood flow. After final dilution the albumin complex concentration of the solution utilized was 20 milligrams per milliliter, and dosage was always kept below 1 milligram per kilogram of body weight. This dosage is well below the critical dose in which the rate of clearance of the albumin complex ceases to be a function of the dose and becomes a function of the fraction of the total blood volume passing through the liver per unit time.

Procedure. All needles, syringes, and 3 way stopcocks used to inject the albumin complex and to obtain samples of blood were meticulously washed in a wetting agent, silicon coated, and sterilized in an autoclave prior to every application. Pipettes and other glassware were washed, kept in a sulfochromic acid solution for 24 hours, rinsed in distilled water, and coated with silicons before each use. All equipment was tested for radioactivity immediately prior to each test. Personnel was required to wear rubber gloves. Established precautions for the handling of radioactive material were employed at all times.

Patients were kept as near to basal conditions as was practical. They remained fasting from the night before and were confined to bed the morning of the test. The body temperature, blood pressure, and pulse

were taken immediately before and after the test. Height and weight were recorded.

A suitable vein in one arm was cannulated with an 18 gauge needle attached to a 3 way stopcock. As a rule it seemed preferable not to use a compression tourniquet on the arm but in those instances in which its application was necessary the tourniquet was removed promptly after venipuncture. It was found that a needle of this rather large size, if properly coated with silicons, could be left in place for more than 10 minutes without becoming obstructed by clots and that suitable samples of blood could be readily obtained from it at the desired intervals. Needles of smaller size, on the other hand, because of their tendency to become obstructed during the course of the test and also because of the slowness attendant on the withdrawal of each 3 milliliter sample, seriously interfered with the timing and accuracy of the test.

With the needle and stopcock securely attached to one arm the radioactive albumin complex was injected as rapidly as possible into a vein of the opposite arm. When the injection of the material was completed blood was aspirated into the syringe and reinjected into the vein. This rinsing of radioactive material from the syringe was considered important particularly when the volume of the dose was small. Volume of the dose injected varied with the normal process of decay inherent in the labelling radioisotope. In order to provide a radioactivity of 20 microcuries, which was found adequate for accurate counting of the samples, it was necessary to use doses of 0.5 to 2 milliliters of the solution of I^{131} albumin complex. In all cases, however, the content of albumin in each dose was not permitted to exceed 1 milligram per kilogram of body weight. Solutions of weaker radioactivity were discarded. Below this critical dosage, clearance of the albumin complex depended not on the size of the dose but on the fraction of the total blood volume perfusing the liver per unit time.

Timing by stopwatch was begun halfway

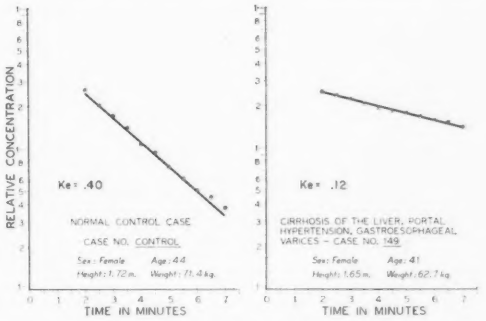
RELATIVE CONCENTRATION
Ke = .40
NORMAL CONTROL CASE
CASE NO. CONTROL
Sex: Female Age: 44
Height: 1.72 m. Weight: 71.4 kg.
TIME IN MINUTES
Ke = .12
CIRRHOSIS OF THE LIVER, PORTAL HYPERTENSION, GASTROESOPHAGEAL VARICES – CASE NO. 149
Sex: Female Age: 41
Height: 1.65 m. Weight: 62.7 kg.
TIME IN MINUTES

FIG. 1. Reproduction of 2 actual clearance curves of I^{131} albumin complex—minimum liver blood flow—corresponding to a normal control case and to a patient with marked decrease in hepatic blood flow.

through the injection of the albumin complex. From the opposite arm, 3 milliliter samples of blood were obtained by way of the 3 way stopcock and deposited in heparinized test tubes. The first sample was obtained at 2 minutes from time zero and from then on at 30 second intervals to complete a total of 11 samples. Withdrawal of each individual sample was accomplished in as short a period of time as possible, and a clean syringe was used for each sample.

Two milliliters of well mixed whole blood from each sample were carefully aspirated into a 2 milliliter blowout pipette and delivered at an extremely slow rate into clean test tubes. The slow delivery left only minute amounts of blood adhering to the wall of the pipette, and these carefully measured samples were counted for 5 minutes in a scintillation well counter (128 scale).

After subtraction of the background registers, the number of registers per sample were plotted on semilogarithmic paper against time in minutes. The kinetic rate of clearance (K_e) was calculated from the equation $\frac{1n_{C1}-1n_{C2}}{T_2-T_1}=K_e$ considering the portion of the curve where the concentration is an exponential function of the time.

To minimize the sources of error hepatic blood flow was not expressed in milliliters per minute but in terms of the kinetic rate of clearance (K_e). Thus, a measurement of the

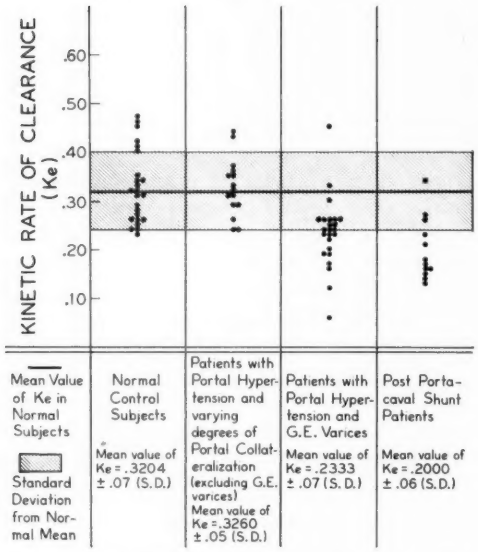
KINETIC RATE OF CLEARANCE (Ke)
.60
.50
.40
.30
.20
.10
Mean Value of Ke in Normal Subjects
Standard Deviation from Normal Mean
Normal Control Subjects
Mean value of Ke = .3204 ± .07 (S.D.)
Patients with Portal Hypertension and varying degrees of Portal Collateralization (excluding G.E. varices)
Mean value of Ke = .3260 ± .05 (S.D.)
Patients with Portal Hypertension and G.E. Varices
Mean value of Ke = .2333 ± .07 (S.D.)
Post Portacaval Shunt Patients
Mean value of Ke = .2000 ± .06 (S.D.)

FIG. 2. Values of the kinetic rate of clearance (K_e) of I^{131} albumin complex—minimum liver blood flow—observed in the 4 groups of patients studied in this investigation.

fraction of the total circulating blood volume cleared by the liver per minute was obtained and used as a comparative value. With the use of this value no correction for body size of the patient was necessary. Results in milliliters per minute could have been obtained by multiplying the value of the blood volume by the value of K_e. Blood volume has been estimated by Biozzi and associates by extrapolating to zero time the clearance of I^{131} albumin complex in plasma and correcting for the hematocrit.

At any rate, since the liver efficiency of colloid clearance is not determined by this test the values obtained should be lower than the values of true liver flow and therefore should be considered as representing minimum liver blood flow.

RESULTS

Hepatic blood flow was determined by using the clearance rate of I^{131} albumin complex in 89 instances in 71 patients. With careful attention to the minute details of the technique satisfactory curves were regularly obtained. Mixing time appeared to be short and before any recirculation of smaller particles or liberated radioactivity took place, a considerable portion of the curve in which concentration was an exponential function of the time was usually available for satisfactory calculation of the value of K_e. Actual clearance curves corresponding to a normal control subject ($K_e = .40$) and to a patient with hepatic cirrhosis, severe portal hypertension, and gastroesophageal varices ($K_e = .12$) are depicted in Figure 1.

Values of K_e in the group of normal control subjects varied within a rather wide range extending from .21 to .47. The mean value of K_e for this group was $.3204 \pm .07$ (S.D.)

Values of K_e in ungrouped patients with varying degrees of portal hypertension and portal collateralization varied within an even wider range extending from .06 to .45. When the values of K_e were compared with the increasing degrees of portal collateralization and portal hypertension described in a previous study (10), no direct correlation could be observed. However, when the patients were grouped according not to the degree but to the type of portal collateralization observed in their splenic portographic studies group tendencies could be discerned (Table I and Fig. 2). In the group of patients in whom hepatic bypass of portal blood was seemingly effected only through vessels communicating with the inferior vena cava (mesenteric, pancreatic, hemorrhoidal, and other portal systemic communications in the abdominal cavity), the values of K_e did not differ from those in the control group (mean value of $K_e = .3260 \pm .05$ S.D.). In the group of patients in whom hepatic bypass was mediated by the gastroesophageal plexuses and the azygos systems into the superior vena cava, the value of K_e was considerably decreased (mean value of $K_e = .2333 \pm .07$ S.D.). Although an occasional individual case departed from this pattern the tendency of the group to the lower values was clear and the difference between the mean value of K_e in this group and that ob-

TABLE I.

Normal control subjects		Patients with portal hypertension and varying degrees of portal collateralization (excluding g. e. varices)		Patients with portal hypertension and g. e. varices		Postportacaval shunt patients	
Case No.	$K\hat{e}$	Case No.	$K\hat{e}$	Case No.	$K\hat{e}$	Case No.	$K\hat{e}$
91	.29	16	.29	11	.26	44	.13
131	.26	19	.24	53	.26	49	.27
136	.32	20	.37	98	.23	55	.15
143	.34	21	.29	100	.19	61	.23
C	.31	36	.35	110	.16	89	.14
C	.47	38	.26	116	.33	98	.18
C	.26	129	.33	125	.24	125	.21
C	.23	133	.36	126	.25	142	.16
C	.28	135	.32	132	.30	154	.34
C	.26	138	.31	137	.23	159	.16
C	.33	145	.43	141	.24	168	.17
C	.46	146	.31	144	.20	170	.26
C	.27	151	.35	148	.19		
C	.21	152	.24	149	.12		
C	.42	165	.44	150	.45		
C	.34			154	.24		
C	.31			155	.22		
C	.40			158	.06		
C	.41			159	.26		
C	.25			169	.17		
C	.32			170	.26		
C	.35			171	.26		
C	.44			172	.23		
C	.24			174	.25		
C	.24						
Mean value of $K\hat{e}$=.3204 S. D.=±.07 S. E.=±.01		Mean value of $K\hat{e}$=.3260 S. D.=±.05 S. E.=±.01		Mean value of $K\hat{e}$=.2333 S. D.=±.07 S. E.=±.01		Mean value of $K\hat{e}$=.2000 S. D.=±.06 S. E.=±.01	

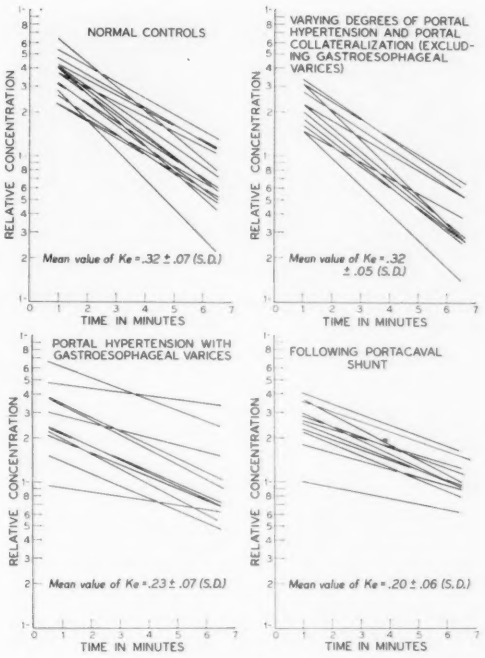
NORMAL CONTROLS
Mean value of Ke = .32 ± .07 (S.D.)
VARYING DEGREES OF PORTAL HYPERTENSION AND PORTAL COLLATERALIZATION (EXCLUDING GASTROESOPHAGEAL VARICES)
Mean value of Ke = .32 ± .05 (S.D.)
PORTAL HYPERTENSION WITH GASTROESOPHAGEAL VARICES
Mean value of Ke = .23 ± .07 (S.D.)
FOLLOWING PORTACAVAL SHUNT
Mean value of Ke = .20 ± .06 (S.D.)
RELATIVE CONCENTRATION
TIME IN MINUTES

FIG. 3. Representative clearance curves of I^{131} albumin complex—minimum liver blood flow. Similarity in the slope of the curve between the 2 groups, upper half, and between the 2 groups, lower half, can be clearly seen.

served in the control group was statistically highly significant ($P<.001$).

When the group of patients submitted to a portacaval shunt was considered, it was found that the value of K_e was lower than in any of the other groups (mean value of $K_e=.2000\pm.06$ S.D.). A direct end-to-side portacaval shunt was performed in 11 of the 12 patients in this group and a splenorenal shunt in the remaining patient. The difference in the mean value of K_e in this group of patients with portacaval anastomosis was highly significant with respect to its value in the control group ($P<.001$), but it did not differ significantly from the already decreased value observed in the group of patients in whom hepatic bypass was effected through gastroesophageal varices ($P>.2$). It should be noted that only 5 patients in the postshunt group had both preoperative and postoperative determinations of hepatic blood flow. The remaining 7 patients in this group had only postoperative determinations.

Representative clearance curves of I^{131} albumin complex corresponding to normal subjects in the control group, to patients with varying degrees of portal hypertension and portal collateralization (excluding gastroesophageal varices), to patients with portal hypertension and gastroesophageal varices, and to patients submitted to a portacaval shunt are presented in Figure 3.

DISCUSSION

Interpretation of the results obtained in this investigation is limited by several factors.

In the first place, any attempt to correlate changes in the portal circulation with values of total hepatic blood flow may be vitiated to an unpredictable extent by the lack of in-

FIG. 4. Film from a multiple exposure serial splenoportogram demonstrating an extreme example of hepatic bypass via the gastroesophageal plexus. Most of the dye injected into the splenic pulp, *1*, is diverted from the liver by huge gastroesophageal varices, *2*. Only a small amount of dye reaches the liver through the portal vein, *3*.

formation on the relative contributions of the portal vein and hepatic artery components of liver flow. It may be that this limitation can only be overcome by direct measurement of flow in the portal vein and in the hepatic artery, a method now being perfected by Schenk and Drapanas and their associates or perhaps, by attempting a separation of flows with a complex combination of tests as has been described by Myers (11). On the other hand, it is possible that evidence obtained by others in the laboratory animal may be used, with the proper reservations, in a tentative interpretation of the phenomena observed in this investigation.

Grayson and Mendel, in 1957, in an article that summarized a series of careful investigations, reported on the intrahepatic flow interactions of the hepatic artery and portal vein of the rat. Under controlled conditions and with the blood pressure of the animals stabilized at levels of 115 to 120 millimeters of mercury, total hepatic blood flow was continuously recorded by the technique of internal calorimetry. It was observed that after suppression of the hepatic artery inflow of the liver a temporary reduction in total hepatic blood flow was produced, but it was also observed that this reduction was shortly followed by a recovery period which brought back hepatic blood flow to near normal values. On the other hand, when the inflow from the portal vein was similarly suppressed a permanent reduction in total hepatic blood flow was observed.

It would appear, therefore, that only changes in the portal vein component of the liver flow are followed by permanent reductions in total hepatic blood flow, and that reductions associated with changes in the hepatic artery contribution are only of a temporary nature. If it could be assumed that these interactions observed in the laboratory animal may also occur in humans, at least a tentative interpretation of the association of decreased total hepatic blood flow and changes in the portal venous system observed in this investigation could be attempted.

According to the results presented in the previous section, the only factor consistently associated with significant decreases in total hepatic blood flow was extensive hepatic bypass of portal blood into the systemic circulation with accompanying reduction in portal vein inflow. In the absence of other evidence it may be tentatively assumed, therefore, that variations in the portal vein contribution to liver flow represented the most important single factor influencing the values of total hepatic blood flow in the patients studied in this investigation.

The degree of diversion of portal blood from the liver varied more with the type than with the number of portal systemic communications observed in these patients. Backflow of portal blood into mesenteric,

pancreatic, retroperitoneal, and other vessels communicating with the inferior vena cava was not associated with any reduction in hepatic blood flow. The efficacy of this backflow as a diverting mechanism and its importance as a factor in reducing the portal vein contribution to liver flow were apparently nonsignificant. On the other hand, the marked reduction in hepatic blood flow associated with diversion through the coronary vein and gastroesophageal plexuses carrying portal blood into the superior vena cava may indicate that the ability of these pathways to reduce portal vein inflow and therefore hepatic blood flow is of a considerably higher magnitude. This could, perhaps, be substantiated by the roentgenographic appearance of these venous structures as observed during splenoportography, an extreme example of which is presented in Figure 4.

Even if no cause-effect relationship should exist between the presence of these different diverting pathways and the corresponding variations in the value of total hepatic blood flow, the association between them would still remain and two main considerations could be derived from it. First, if a surgical portacaval shunt is established in patients with gastroesophageal varices the small further decrease in the already diminished hepatic blood flow may not add significantly to the long-standing metabolic derangement of these patients. Secondly, if a direct end-to-side portacaval shunt is constructed in the absence of gastroesophageal varices, i.e., for the treatment of ascites, the normal rate of hepatic blood flow observed in patients of this type may be sharply decreased and symptoms of greater severity may ensue.

Finally, it should be mentioned that there are certain technical limitations inherent in the method of determining hepatic blood flow used in this investigation, the main one being that a specific localization of the colloid in the liver and the spleen must be assumed. This assumption, at least with respect to the experimental localization of I^{131} albumin complex, appears to have been confirmed by Benacerraf and associates as well as by studies in dogs conducted in this laboratory, where a 91 per cent concentration of this material was shown to occur in the liver. Other assumptions involving the efficiency of removal of the colloid and the validity of using the initial portion of the clearance curve to establish the value of the kinetic rate of disappearance seem to have been corroborated both by the work of other investigators and by the regularity and absence of "tailing" of the curves obtained in these studies.

SUMMARY AND CONCLUSIONS

1. Correlation between changes in portal hemodynamics and values of total hepatic blood flow has been limited in this investigation by the lack of information on the arterial component of liver flow. In the absence of practical techniques to assay this arterial aliquot in unanesthetized human subjects the available evidence collected by others in the experimental animal has been used in a tentative interpretation of the phenomena observed in the patients in the present series.

2. Within the limitations of this tentative interpretation it would appear that variations in the portal vein contribution to liver flow represented the most important single factor influencing the values of total hepatic blood flow.

3. Variations in portal vein contribution to liver flow seemed to depend exclusively on the extent of hepatic bypass of portal blood into the systemic circulation.

4. The extent of hepatic bypass apparently varied more with the type than with the number of portal systemic communications observed in these patients. Backflow into the coronary vein and gastroesophageal plexuses carrying portal blood into the superior vena cava was the only type of hepatic bypass associated with decreased total hepatic blood flow, whereas backflow into mesenteric, pancreatic, and other vessels emptying into the inferior vena cava was not associated with any changes in hepatic blood flow.

5. If a surgical portacaval shunt is established in patients with gastroesophageal varices the small further decrease in the already diminished hepatic blood flow may not add significantly to the long-standing metabolic derangement of these patients.

6. If a direct end-to-side portacaval shunt is constructed in the absence of gastroesophageal varices, i.e., for the treatment of ascites, the normal rate of hepatic blood flow observed in patients of this type may be sharply decreased and symptoms of greater severity may ensue.

7. Certain technical limitations inherent in the estimation of hepatic blood flow by the colloid clearance method did not appear to have influenced the comparative value of this determination in the different groups of patients studied in this investigation.

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TUMORS OF THE PARATHYROID GLANDS FOUND INCIDENTALLY DURING SURGICAL PROCEDURES

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In 1947, for the first time at the Mayo Clinic a typical parathyroid adenoma was discovered by chance during the course of a thyroidectomy. From that occasion through 1958, a total of 20 adenomas and 1 instance of wasserhelle hyperplasia have been encountered during surgical procedures undertaken for other objectives. One of the cases has been reported in brief by Ogburn and Black, and 4 have been reviewed in a recent report by Randall and Keating. To our knowledge, the chance finding of a parathyroid tumor during a surgical procedure other than an exploration of the parathyroid glands has not been reported otherwise.

The removal of palpable cervical tumors that proved to be parathyroid adenomas has been reported. Keynes, Cope, and Hadfield and Rogers each have reported a single such case. Among Norris' collection of 322 cases of parathyroid adenoma from the literature were 5 without complications of hyperparathyroidism. It is not clear whether the tumors were palpable or whether hyperparathyroidism was recognized before operation.

The fortuitous recognition of hyperparathyroidism before the development of urinary or osseous complications is becoming increasingly commonplace. Randall and Keating have reviewed recently the experience at the clinic with the fortuitous diagnosis of hyperparathyroidism during the investigation of unrelated conditions. Four cases in the present series were included in their report, as previously mentioned. In the other 16 cases in their series, values for serum calcium had been initially determined preoperatively with some condition other than hyperparathyroidism in mind.

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MATERIALS AND METHODS

Collection of data. The 21 cases that comprise the subject of this report differ from the other 318 cases of tumors of the parathyroid glands in the clinic series, through 1958, in that among all cases of the latter group the diagnosis of hyperparathyroidism was established before operation. The presently reported instance of wasserhelle hyperplasia was discovered during excision of a pharyngoesophageal diverticulum. In the other 20 cases, the thyroid gland afforded the primary reason for surgical intervention. The thyroidal disorder was representative of nontoxic nodular goiter in 10 cases, toxic nodular goiter in 1, Hashimoto's thyroiditis in 3, exophthalmic goiter in 2, and papillary carcinoma of the thyroid in 4.

In this series of 21, the possibility of hyperparathyroidism was not considered, and determinations of serum calcium were not made before operation, nor was any tumor of the parathyroids palpable. Blood was drawn for determinations of calcium and usually of phosphate during or immediately after the surgical procedure in 19 cases. In 1 case, the first determinations were made several days later; in 1 other, the values for calcium and phosphate were not determined either before or after removal of an oxyphilic adenoma. Except for this latter case, calcium levels were determined at least twice and frequently more than twice during the week or so next after operation.

After discovery of the lesion in the parathyroids, every patient was questioned care-

TABLE I. — HYPERPARATHYROIDISM PROBABLY NOT PRESENT

Case	At operation* Ca†	At operation* P†	After operation Ca†	After operation P†	Pathologic findings	Tumor weight, mgm.
1	9.0	4.6	7.6	5.0	Chief cell adenoma	150
2	9.4	2.7	7.9	2.7	Chief cell adenoma	510
3	9.4	2.7	8.8	2.8	Chief cell and transitional wasserhelle adenoma	420
4	9.6	4.7	9.7	3.5	Chief cell adenoma	70
5	9.9	3.6	8.8	—	Mixed oxyphilic and transitional wasserhelle adenoma	300
6	9.9	3.5	9.5	—	Chief cell adenoma	—
7	9.9	3.3	7.4	4.5	Chief cell adenoma	480

*Or immediately thereafter.
†Mgm. per 100 ml. serum.

TABLE II.—PRESENCE OR ABSENCE OF HYPERPARATHYROIDISM NOT CLEAR

Case	At operation* Ca†	At operation* P†	After operation Ca†	After operation P†	Pathologic findings	Tumor weight, mgm.
8	—	—	9.6	3.0	Mixed chief and oxyphilic adenoma	—
9	—	—	—	—	Oxyphilic adenoma	170
10	10.0	2.2	8.7	3.7	Chief cell and transitional wasserhelle adenoma	860
11	10.1	—	9.7	3.3	Chief cell adenoma	170
12	10.2	3.9	9.6	3.3	Mixed chief cell and oxyphilic adenoma	300
13	10.3	3.0	8.6	3.8	Transitional wasserhelle adenoma	250

*Or immediately thereafter.
†Mgm. per 100 ml. serum.

fully for symptoms that might be attributable to hyperparathyroidism. The urinary tract and skeleton were investigated further when such studies seemed indicated. No symptoms of hyperparathyroidism were found and no generalized osteitis fibrosa cystica was demonstrated. Two patients, neither of whom had urinary lithiasis when the tumor was found, had passed stones previously. One of these 2 patients, Case 19, had hyperparathyroidism that could have been diagnosed unequivocally before operation if the levels of calcium and phosphate had been determined then. This case emphasizes the fact that in the recognition of hyperparathyroidism a history of passing stones has the same importance as the presence of stones. In the other of the 2 patients, hypercalcemia was not indicated by the single determination of the serum calcium value.

Presence of hyperparathyroidism. In the complete absence of symptoms, the presence or absence of hyperparathyroidism necessarily was established by the single immediate determination of serum calcium and phosphate. In the 2 cases in which such determinations were not carried out, the question of hyperparathyroidism could not be considered. Any marked change in calcium and phosphate values after operation probably can be given little weight, since one or more of the remaining parathyroids may have been resected or devascularized during the surgical procedure. This seems the most plausible explanation of the marked postoperative decline of the calcium level in Cases 1, 2, 7, and 17.

With allowance for the factors of uncertainty mentioned, hyperparathyroidism was considered to be absent in cases 1 through 7 (Table I). The values for phosphate were low in Cases 2 and 3 but not beyond the range for normal individuals in our laboratory. The relatively low levels of calcium in those 2 cases make hyperparathyroidism most improbable.

In Cases 8 through 13 (Table II), the presence or absence of hyperparathyroidism could not be evaluated. In 2 the calcium values were not determined and in 4 they were equivocal. Hyperparathyroidism can exist and has been recognized at the clinic and elsewhere in cases in which the value for serum calcium was less than 10.4 milligrams per 100 milliliters. In some cases of minimal hypercalcemia, the levels of serum phosphate may be within or near the lower limits of the normal range. Absence of hyperparathyroidism may not be inferred with assurance from the normal levels of phosphate in Cases 12 and 13. Needless to add, more extended studies before removal of the adenomas might better have resolved the problem.

In the remaining cases (Table III), the available evidence favors the view that hyperparathyroidism was present. The mean value for serum calcium in normal individuals as determined at the clinic is 9.77 milligrams, and 95 per cent of values from normal persons lie between 9.4 and 10.3

milligrams. Thus all patients in this third group definitely had hypercalcemia. The normal levels of phosphate in Cases 15, 18, 20, and 21 are not incompatible with the diagnosis of hyperparathyroidism. It has been recognized for some years that serum phosphate may be normal without impairment of renal function in cases of proved hyperparathyroidism. Cases of this type have been discussed at some length by Goldman and associates. The phosphate value of 4.4 in Case 17 most probably is erroneous, since the same value was found postoperatively at a time when the calcium level had fallen from 11.2 to 7 milligrams.

Except for Case 17, as previously mentioned, the postoperative decline of calcium values in this group probably is as strong evidence of hyperparathyroidism as is the hypercalcemia. At least the magnitude and rate of decline are entirely in keeping with the changes in calcium values after removal of hyperfunctioning adenomas reported elsewhere.

Pathologic findings. As shown in the tables, a single parathyroid adenoma was present in 20 cases, and in 1 case the pathologic diagnosis was primary wasserhelle hyperplasia. Grossly the adenomas were typical, being yellowish-brown to dark brown, encapsulated, and nonadherent to surrounding structures. Their weight varied from 70 milligrams to 900 milligrams, the average being 378 milligrams. Tumors no larger than this are associated commonly with symptoms of primary hyperparathyroidism. In a previously reported (9) series of 140 cases of primary hyperparathyroidism, 40 adenomas were found to weigh less than 1 gram and 24 of these weighed less than 500 milligrams.

Histologic examination of the 20 adenomas in our series showed that 7 were composed largely of chief cells, 1 of small transitional wasserhelle cells, and 1 of pale oxyphilic cells. The remainder exhibited mixtures of cell types. Typical examples are shown in Figures 1 and 2. There was no demonstrable difference in cell type between those adenomas associated with elevated values for serum calcium and those associated with normal calcium values. Oxyphilic cells, often stated to be nonfunctioning, were not a prominent feature of either group. No examples of large wasserhelle cell adenoma were found in the series. It is unfortunate that the levels of calcium and phosphate were not determined in the 1 case of the patient with oxyphilic adenoma, Case 9.

TABLE III.—HYPERPARATHYROIDISM PROBABLY PRESENT

Case	At operation*† Ca†	At operation*† P†	After operation† Ca†	After operation† P†	Pathologic findings	Tumor weight, mgm.
14	10.6	—	9.5	2.9	Mixed chief and transitional wasserhelle adenoma	—
15	11.1	3.1	8.6	3.0	Mixed chief and transitional wasserhelle adenoma	—
16 a	—	—	11.1	1.4	Wasserhelle hyperplasia	—
b	11.3	1.9	9.1	3.2	Wasserhelle hyperplasia	>6200
17	11.2	4.4	7.0	4.4	Mixed chief and oxyphilic adenoma	650
18	11.4	3.3	10.1	4.2	Chief cell adenoma	340
19	11.4	2.4	8.2	2.6	Mixed chief cell and transitional wasserhelle adenoma	—
20	11.6	2.7	8.2	3.0	Mixed chief cell and transitional wasserhelle adenoma	460
21	11.7	2.8	8.4	3.0	Transitional wasserhelle cell adenoma	900

*Or immediately thereafter.
†Mgm. per 100 ml. serum.

In Case 16, all parathyroid tissue resected had the classic appearance of wasserhelle hyperplasia, with large clear cells arranged in an alveolar acinic pattern (Fig. 3). So far as we know, this is the first reported case of primary wasserhelle hyperplasia in which "chemical hyperparathyroidism" was the only related abnormality noted to be present.

Usually wasserhelle hyperplasia is characterized by greater bulk of tissue than is adenoma. In 12 cases previously reported from this institution (9), the weight of resected parathyroid tissue averaged 19 grams and varied from 760 milligrams to 52.5 grams; only three of the specimens weighed less than 5 grams.

The case of wasserhelle hyperplasia in this series is of sufficient interest to report in some detail.

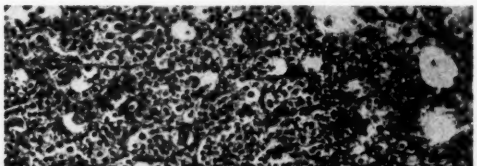

FIG. 1. Case 17. Parathyroid adenoma of predominantly chief cell type. Calcium values elevated. Hematoxylin and eosin, ×133.

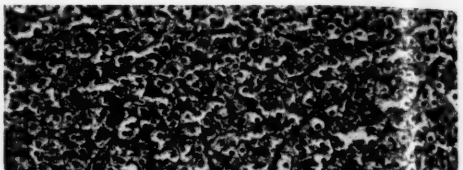

FIG. 2. Case 13. Parathyroid adenoma composed of chief cells with granular, somewhat acidophilic cytoplasm. Hematoxylin and eosin, ×133.

CASE 16. The patient was a woman of 57 who had had increasing dysphagia for 2 years. The cause proved to be a pharyngoesophageal diverticulum, and excision was advised. During the course of the diverticulectomy, a mass of tissue measuring 2 by 1 by 1 centimeters was removed. Microscopic examination revealed typical wasserhelle hyperplasia. No other parathyroid tissue was found in the operative field. The weight of the resected tissue was not determined, nor were the values for serum calcium and phosphate determined immediately. Twenty-four hours after operation they were 11.1 and 1.4 milligrams, respectively, per 100 milliliters of serum. Extensive questioning of this patient failed to elicit any symptoms that could be attributed by the physician to hyperparathyroidism.

Two months later, the chemical values remaining essentially unchanged at 11.3 and 1.9 milligrams, formal exploration of the parathyroids was carried out. No parathyroid tissue was found on the left side, which had been exposed at the earlier procedure. The two parathyroids on the right side were found without difficulty. The superior gland, which measured 3.5 centimeters in its greatest diameter and weighed 6 grams, was removed completely. The much smaller right inferior gland was resected subtotally, leaving an estimated 100 milligrams of viable tissue. The resected part of the gland was found to weigh 200 milligrams.

Forty-eight hours later the level of calcium had fallen to 9.1 and that of phosphate had risen to 3.2 milligrams. Subsequently the values for calcium remained between 8.7 and 8.6 milligrams and those for phosphate between 3.0 and 3.3 milligrams per 100 milliliters of serum. Since the hyperparathyroidism was cured, it was assumed that the solitary mass of hyperplastic tissue removed from the left side at the original surgical procedure must have represented both left parathyroids.

COMMENT

The history of hyperparathyroidism illustrates the dictum that the more diligently a given disease is sought, the more often it is found. In the classic form in which primary hyperparathyroidism was originally identified—namely, that associated with osteitis fibrosa cystica—the condition is extremely rare and might not be encountered once in the lifetime of the ordinary physician. After the brilliant observations of Albright led to realization that the condition occurs more often in the absence than in the presence of clinically evident bone disease and that sometimes renal lithiasis is its only manifestation, primary hyperparathyroidism was diagnosed much more frequently. Estimates of its frequency have been various and unreliable, but some figures have indicated that as many as 5 per cent of patients with renal stones may be found to have this condition. A series of cases recently reported by Randall and Keating as well as those included in this report emphasize the fact that neither renal disease nor osseous disease is a necessary concomitant of primary hyperparathyroidism and that, indeed, the condition may and does exist in the absence of any clinical symptoms whatever. A corollary is that there is no basis at present for even a provisional estimate of the incidence of this disturbance.

In 7 of the 21 cases we have reported (Table I), neither chemical nor clinical evidences of primary hyperparathyroidism were present. It is noteworthy that in 6 of these 7 cases the postoperative values for serum calcium were at least slightly below preoperative ones, and in 4 cases the difference exceeded 1 milligram. Histologically the tumors from these 7 cases resembled those from cases in which chemical evidence of hyperparathyroidism was present (Table III), and both groups were similar histologically to tumors from typical cases of primary hyperparathyroidism having the usual consequences in kidneys or bones. We suspect, therefore, that these may have been functioning parathyroid tumors even though by the criteria currently in vogue they were not hyperfunctioning. But although it is inviting to ascribe the minor perturbations of serum calcium in these 7 patients to the effect of removing a functioning tumor, the effect of surgery upon the functional integrity of the nonadenomatous, uninvolved parathyroids might also have been responsible.

The 8 patients represented in Table III may be regarded with reasonable certainty as having "chemical hyperparathyroidism." Study of their renal and osseous systems revealed no signs or symptoms referable to primary hyperparathyroidism or its secondary effects. Together with 5 other cases reported by Randall and Keating, these make a total of 13 instances of "chemical hyperparathyroidism" without clinical manifestations to have been identified at this institution.

The very manner in which these cases were found makes clear that too little is known of their calcium metabolism to support a prediction of what might have happened if the tumors had been left in situ. Would the tumors unassociated with chemical evidence of hyperparathyroidism have produced such evidence in time? Would those associated with chemical hyperparathyroidism but without symptoms have produced symptoms eventually? Neither question can be answered. The hazard of clinically significant osseous involvement is probably a contingency too remote for serious consideration. However, the possibility of eventual renal damage from calculi or nephrocalcinosis is more difficult to assess. In Case 13 of the Randall and Keating series, asymptomatic hypercalcemia was observed for 11 years, after which serious nephrolithiasis and an intractable duodenal ulcer appeared for the first time. It seems best to proceed on the assumption that hyperparathyroidism, both latent and chemical, is clinically important and deserves treatment because of the jeopardy to renal function.

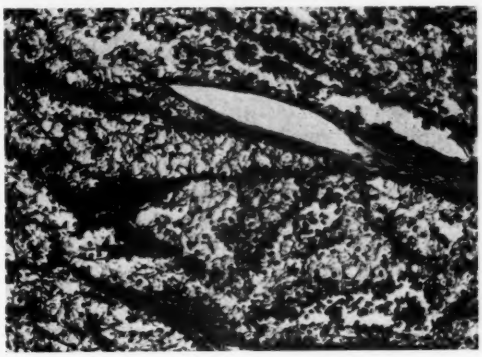

FIG. 3. Case 16. Diffuse wasserhelle hyperplasia. Hematoxylin and eosin, ×133.

SUMMARY

During the 12 year period from 1947 through 1958, 20 parathyroid adenomas and 1 instance of wasserhelle hyperplasia were found fortuitously during surgical procedures at the Mayo Clinic. All of the adenomas were discovered during thyroidectomy; the hyperplasia was encountered during removal of a pharyngoesophageal diverticulum. None of the patients had symptoms or complications of hyperparathyroidism. Determinations of serum calcium and phosphorus indicated that hyperparathyroidism was probably absent in 7 cases and probably present in 8; in 6 cases the chemical findings were equivocal or the determinations were not made. There was

no demonstrable difference of cell types between the adenomas thought to be hyperfunctioning and those associated with normal levels of serum calcium, nor was there any difference between the adenomas in the present series and others known to be associated with clinical hyperparathyroidism. Although the evidence was not conclusive, the chemical findings from the 7 cases in which hyperparathyroidism was not manifest did suggest that the adenomas were functioning, but clearly not to the extent of producing chemical hyperparathyroidism.

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INTERSCAPULOTHORACIC AMPUTATION AND SACROILIAC DISARTICULATION WITH ADJUNCTIVE ARTERIAL CHEMOTHERAPY

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MANY of the major extirpative procedures used today in the treatment of cancer were first carried out at or near the turn of the century. These operations have persisted with only minor variations because they were logically planned as cancer operations based on sound anatomic and pathologic principles. Forequarter and hindquarter amputations fall into this category and are sometimes grouped together under the term quarterectomy.

Forequarter or interscapulothoracic amputation is defined as the removal of the entire upper extremity and the shoulder girdle with all muscular attachments along with the contents of the axilla and supraclavicular area of the neck. The first successful procedure for tumor was performed in 1836. In 1887 Berger reviewed the previous literature and standardized the technique used with some variation today. The mortality rate in a recently reported series by Pack and Ariel is less than 5 per cent and the over-all 5 year survival rate ranges from 25 to 35 per cent.

Hindquarter amputation, sacroiliac disarticulation, or hemipelvectomy, as the procedure is most commonly called, is defined as the complete removal of the lower extremity, buttock, and innominate bone along with the contents of the femoral, inguinal, and iliac node-bearing areas. It was first attempted in the treatment of malignant disease by Billroth in 1891. The first successful operation was carried out by Girard in 1895. In 1916 Pringle reported 4 cases and standardized the technique used today. The mortality rate in recently reported series is less than 10 per cent and the over-all 5 year survival rate for all types of neoplasm ranges from 20 to 25 per cent.

Despite the fact that these two procedures are now technically possible with very low mortality and morbidity rates, they are still performed too frequently as a last resort procedure. In our cases this can seldom be laid to the patient, who usually is already disabled because of pain, deformity, and dysfunction of the extremity. In many instances the family physician and surgeon both are reluctant to advise the operation until it is performed as an operation of desperation. The surgeon who unhesitatingly will carry out radical extirpation of a cancer in other areas will be content with simple excision of a sarcoma of the extremity.

MATERIALS AND METHODS

The series reported here consists of 11 forequarter amputations and 9 hemipelvectomies. All were performed for malignant disease of the extremity (Table I). There were 12 males and 8 females. Ages ranged from 9 to 75 years. The longest surviving patient has now lived 3 years and 2 months since the amputation. Arteriograms were made by using sodium acetrizoate with films taken on a Sanchez-Perez automatic seriograph. Chemotherapeutic agents used were nitrogen mustard and dimethyl myleran injected intra-arterially early in the procedure through polyethylene catheters.

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TABLE I.—MATERIAL

	No.	Positive nodes	Local recurrence	Pulmonary metastases	Living
Rhabdomyosarcoma	7	0	0	5	4
Osteogenic sarcoma	4	1	1	3	2
Fibrosarcoma	2	0	0	1	1
Neurofibrosarcoma	1	0	1	1	0
Malignant schwannoma	1	0	0	0	1
Liposarcoma	1	0	1	0	1
Squamous cell carcinoma	1	1	1	1	0
Ductal carcinoma (breast)	1	1	0	0	1
Undifferentiated sarcoma	1	0	Operative death		0
Melanoma	1	1	Operative death		0
Total	20	4	4	11	10

INDICATIONS

Following are the indications for the operation:

1. The lesion and limb which is cumbersome, painful, foul smelling, hemorrhaging, and intolerable to the patient and to those who care for him. Palliative resection may in some cases be carried out in the presence of metastases if they are small and not disabling in themselves.

2. Some relatively benign tumors involving the shoulder or hip which grow to huge size, are disabling, and may become malignant. The most common of these is the chondroma.

3. Infiltrating tumors of the shoulder girdle or of the hip or pelvis with no evidence of distant spread.

4. Tumors of axilla or groin which are adherent to vessels, nerve plexuses, or other adjacent structures which technically cannot be removed with a lesser procedure.

5. Malignant tumors of the humerus and of the upper femur in all cases.

6. Infiltrating soft tissue malignant tumors of the arm or the thigh which cannot be successfully treated by removal of the entire muscle group involved.

TABLE II.—SUMMARY

	Forequarter (11 cases)	Hindquarter (9 cases)
Average age, yrs.	45.6 (9–75)	45.8 (15–70)
Previous treatment	8	8
Preoperative duration	2 to 24 mos.	1 mo. to 19 yrs.
Positive nodes	2	2
Palliative	5	4
Recurrence		
Local	2	2
Pulmonary	5	6
Average operating time	1 hr. 59 min.	2 hrs. 5 min.
Surgical mortality	1 (9 per cent)	1 (11 per cent)
Average postop. hospital days	9 (6–18)	18 (15–23)
Living	6 (1 with rec.)	4 (3 with rec.)
Survival time, mos.		
Those dead	0–2–7–8–4 Av. 4	0–4–5–5–19 Av. 6⅓
Those living	7–10½–12–18–36–38 Av. 20½	14–16–18–23 Av. 18

TECHNIQUE

Interscapulohumeral amputation. In general, we perform the classical Berger operation using a racquet incision with the linear extension parallel to and above the clavicle. Both the anterior and posterior approaches have been used. When adjunctive chemotherapy has been used, the anterior approach has been the rule. If the clavicle is involved in tumor, it is disarticulated at the sternal joint and removed in its entirety. Otherwise it is divided at the junction of the proximal and middle thirds and reflected to expose the subclavian vessels. The pectoral muscles are divided and retracted laterally to give complete exposure of the vessels. Both artery and vein are mobilized and sutures are passed around them but not tied. A polyethylene catheter is then passed a short distance into the artery distally. The vein is obstructed and the chemotherapeutic agent injected into the tubing. Both artery and vein are doubly ligated and divided. The remainder of the procedure is carried out in a traditional fashion. The brachial plexus is ligated with plain catgut and is divided with a sharp knife. The incision is closed around two Robinson catheters for suction drainage.

The use of chemotherapy in an extremity which has its major venous return blocked may be questioned. It has been shown that tumor cells are frequently found in the general circulation even before surgery. The viability of these cells is not known, nor are the factors which encourage seeding and growth in a new area. During surgery the actual number of tumor cells in the circulation frequently increases. Thus it appears desirable to block the major venous return

TABLE III.—SUMMARY OF PATIENTS WITH ADJUVANT CHEMOTHERAPY

Case No.	Age, yrs.	Diagnosis	Location	Surgery	Chemotherapy: During operation	Chemotherapy: After operation	Complications	Pulmon. metast.	Response
1	9	Osteogenic sarcoma	Rt. humerus, shoulder girdle	Right fore-quarter	Dimethyl myleran, I.A.	0	0	Yes	Died 2 mos.
2	43	Osteogenic sarcoma	Rt. hand, rt. axilla	Right fore-quarter	Nitrogen mustard, I.A.	0	0	0	Living 12 mos.
3	71	Ductal ca. (breast)	Left axilla	Left fore-quarter	Nitrogen mustard, I.A.	0	0	0	Living 10½ mos.
4	63	Rhabdomyo-sarcoma	Left shoulder	Left fore-quarter	Nitrogen mustard, I.A.	0	0	0	Living 7 mos.
5	15	Osteogenic sarcoma	Right femur	Right hind-quarter	Dimethyl myleran, I.A.	Nitrogen mustard, I.V.	Hemothorax marrow depression	Yes	Living 18 mos. with rec.
6	30	Rhabdomyo-sarcoma	Left thigh	Left hind-quarter	Dimethyl myleran, I.A.	0	0	Yes	Living 16 mos. with rec.
7	70	Melanoma	Rt. foot, leg, groin	Right hind-quarter	Nitrogen mustard, I.A.	0	0	0	Operative death

from the involved extremity as early in the operation as practical. The addition of arterial chemotherapy might be expected to damage cells which later break loose and enter the general circulation through alternate venous routes. In addition, such chemotherapy reaches the anatomic distribution of the artery which is somewhat greater than the limits of the surgical margins. Such arterial chemotherapy is enhanced by having the venous drainage blocked. Because the chemotherapeutic agent is largely limited to the extremity to be removed, there are no contraindications to using supplementary systemic chemotherapy preoperatively or postoperatively.

Sacroiliac disarticulation. The technique of this procedure has been described by several others. The iliac vessels are exposed through the inguinal portion of the incision before other dissection is carried out. Tapes are passed around the artery and vein for control, and a polyethylene catheter is inserted into the artery. Arteriograms are taken when indicated. The chemical agent is injected via the catheter with the vein occluded, after which the common iliac vessels are ligated and divided. Ligation of the common iliac rather than the external iliac vessels has not resulted in any loss of posterior skin flap. It has the advantages of permitting better iliac node dissection and of less blood loss later in the procedure. The pubic symphysis is divided with knife or Gigli saw. Care must be taken to avoid injury to the dorsal vein of the penis, ureter, bladder, rectum, and urethra. There is usually a certain amount of bleeding from the retropubic venous plexus. This can be controlled by a pack at this time. Ligation of individual vessels may be more easily carried out later after removal of the limb. An extra 200 to 300 cubic centimeters of transfused blood prior to this phase will avert a fall in blood pressure. If the location of the tumor permits, the gluteus maximus muscle may be left attached to the posterior flap. The sacroiliac joint can be divided from either anterior or posterior aspect. It has been our practice to divide it just beyond the joint from behind with a Gigli saw. This is the second point where anticipation of blood loss by a transfusion of 200 to 300 additional cubic centimeters of bank blood will help to keep the patient stabilized. All incisions are closed with 2 Robinson catheters for suction drainage of the stump.

TABLE IV.—SUMMARY OF PATIENTS WITHOUT ADJUVANT CHEMOTHERAPY

Case No.	*Age, yrs.*	*Diagnosis*	*Location*	*Surgery*	*Complications*	*Pulmonary metastases*	*Response*
8	40	Rhabdomyosarcoma	Lt. arm	Left forequarter	0	Yes	Died 4 mos.
9	34	Neurofibrosarcoma	Upper lt. arm	Left forequarter	Severe phantom pain	Yes	Died 8 mos.
10	75	Rhabdomyosarcoma	Rt. upper humerus	Right forequarter	0	0	Living 38 mos.
11	49	Malignant schwannoma	Rt. elbow region	Right forequarter	0	0	Living 36 mos.
12	62	Undifferentiated neoplasm	Rt. shoulder	Right forequarter	Myocardial infarction	0	Dead 6th P.O. day
13	55	Liposarcoma	Rt. arm	Right forequarter	0	Yes	Living 18 mos.
14	32	Rhabdomyosarcoma	Rt. shoulder	Right forequarter	0	Yes	Dead 7 mos.
15	63	Rhabdomyosarcoma	Rt. thigh	Right hindquarter	0	Yes	Dead 4 mos.
16	41	Fibrosarcoma	Lt. leg	Left hindquarter	0	Yes	Dead 19 mos.
17	51	Fibroliposarcoma	Rt. upper thigh	Right hindquarter	0	0	Living 23 mos.
18	38	Rhabdomyosarcoma	Rt. groin	Right hindquarter	0	Yes	Living 14 mos.
19	28	Squamous cell ca.	Rt. leg	Right hindquarter	0	0	Dead 5 mos.
20	64	Osteogenic sarcoma	Rt. femur	Right hindquarter	0	Yes	Dead 5 mos.

DISCUSSION

Indications. The total number of these operations reported is small. Pack and Ariel collected less than 300 hemipelvectomies from the world literature. The individual series do not lend themselves well to evaluation and standardization of the indications. Our own belief is that indications cannot be too standardized at present because of the wide diversity of type, location, and size of the tumors. The proper approach requires individualization of each case in the light of an adequate cancer operation—one in which the primary tumor and the organ in which it is growing, the regional lymph nodes, and the intervening lymphatics are removed en masse. The lymph nodes and lymphatics appear to be much more significant in the spread of melanoma and carcinoma than of sarcoma. In this field of surgery there are several important points which should be emphasized.

1. Simple shelling out of the tumor or wedge excision is not adequate. This fact is attested to by the high incidence of local recurrence following these limited procedures.

2. In soft tissue malignant tumors, the entire muscle group involved must be removed along with adjoining fascial planes. Nerves and vessels entering these contaminated spaces must be sacrificed.

3. Any bone involved should be removed in its entirety.

4. Bone tumors which break through into soft tissue will behave and spread along soft tissue planes as well as subperiosteally and in the marrow cavity. Conversely, soft tissue tumors involving bone will spread through the marrow cavity. Thus a bone or muscle that is involved secondarily must be removed in its entirety.

5. Many of these tumors appear to become more malignant with each local recurrence.

6. The argument that sarcomas do not

FIG. 1. FIG. 2. FIG. 3.

FIG. 1. Arteriogram showing increased vascular pattern characteristic of osteogenic sarcoma in Case 1.
FIG. 2. Arteriogram showing vascular pattern of soft tissue sarcoma in Case 3.
FIG. 3. Arteriogram showing vascular pattern of osteogenic sarcoma in Case 5.

metastasize to lymph nodes is not correct. Various series report regional node metastases to range from 10 per cent for fibrosarcoma to 50 per cent for angiosarcoma. In our own series, the over-all incidence of positive nodes present at the time of surgery is 20 per cent. If one eliminates the carcinomas and melanoma the incidence of node involvement is 6 per cent.

If these principles of adequate excision of the tumor and its potential avenues of spread cannot be met by a lesser procedure, then quarterectomy should be carried out.

The question sometimes arises as to joint disarticulation. In the shoulder this is not indicated. The forequarter is safer, a more adequate cancer operation, and only equally disabling. The shoulder without the arm is of cosmetic value only as a coat hanger. In the hip, the issue is not so clear. However, the tendency to do disarticulation as a lesser procedure should be thoughtfully considered (and each case individualized) in the light of these advantages of hemipelvectomy: (1) Femoral, inguinal, and iliac nodes are removed in combination with the tissues making up their beds. (2) Nerves and vessels are removed at a higher level. (3) All involved muscle and fascial planes are removed in their entirety. (4) The disability is greater but the hip joint is lost in both cases. (5) Morbidity and mortality are essentially the same.

Morbidity and mortality. There was 1 operative death in the series of 11 forequarter amputations. The patient was a 62 year old white male who had a palliative forequarter amputation for a massive reticulum cell sarcoma of the right shoulder girdle. He died on the sixth postoperative day of a myocardial infarction. There were no other early complications and all wounds healed primarily. Four patients had phantom limb pain. Two of these cases were not clinically significant, being mild and transient, and no treatment was necessary. The other 2

were of moderate degree but persistent, and analgesics were required for control. In 1 of these there was persistent tumor around the stumps of the brachial plexus.

There was also 1 operative death in the series of 9 hindquarter amputations. The patient was a 70 year old white male who had had a palliative hemipelvectomy for melanoma of the foot involving the entire leg. It was considered palliative because there was 1 small suspicious lesion in the lung. He died on the eleventh postoperative day of a massive pulmonary embolus. All patients with hemipelvectomy had primary wound healing despite the fact that in 6 of 9 cases the common iliac vessels were ligated rather than the external iliac vessels. Persistent ileus did not develop in any instance. One 63 year old white female required a Foley catheter for 14 days but had no further difficulty with urination. In no case did anemia requiring transfusion develop. Phantom pain was present in only 1 patient. This patient had recurrent tumor in the periaortic and retroperitoneal lymphatics.

Results. The significant data for our series are summarized in Table II. Since we have been carrying out these procedures only during the last 4 years, 5 year survival figures are not available. Of 11 patients with forequarter amputations, 6 are still living, 5 without evidence of disease. As can be seen in Table II, 3 of 4 patients who had hemipelvectomies are dead after 4, 5, and 5 months. The average survival period of those living is 18 months. Similarly, 4 of 5 patients who had forequarter amputations died at 9 months or less, while the average survival time of those living is 20½ months.

The factors which may affect survival are not clearly shown in this group. Sixteen of the 20 patients had had previous treatment of some type. Preoperative duration of the lesion varied from 1 month to 19 years and there was no definite correlation with postamputation survival.

Four of 20 patients (with sarcoma and carcinoma), or 20 per cent of the total, had tumor in the regional nodes at the time of quarterectomy. Of these 4 patients, only 1 has survived 10½ months without evidence of recurrence.

In our series there was a high percentage of palliative cases, 9 of 20 cases being in this category. The average postoperative survival period was 6.6 months. One patient survived 19 months. Since all palliative operations were performed for massive, painful bleeding, or fungating tumors, we believe that this management represents significant palliation in terms of comfort and ease of care.

Local recurrence in the operative field occurred in 4 of the 20 cases. In 2 of these the operations had been palliative but 2 had been considered curative. Pulmonary metastases occurred in 55 per cent of the cases (Tables I, II, and IV). Six of the 11 occurred in the patients who had had hemipelvectomies and 5 in those who had undergone forequarter amputations. The majority of these metastases occurred in patients with rhabdomyosarcoma, osteogenic sarcoma, and fibrosarcoma (Table I). Both local recurrence and pulmonary metastases occurred in 2 patients who had had hemipelvectomy. In 3 of the 7 patients who received adjuvant chemotherapy, pulmonary metastases developed (Table III).

Adjuvant chemotherapy. All too often, surgical excision is successful in locally eradicating tumor, only to have distant metastases appear. Whether these are present prior to surgery, whether they represent seeding associated with surgical trauma, or whether they are due to altered host resistance cannot be established at this time. In any case, metastases were not clinically apparent at the time of operation. Certainly, evidence suggests that showers of tumor cells may be seen in the blood stream at the time of operation. This observation has led to the use of chemotherapeutic agents at the time of and subsequent to operation in an attempt to prevent these cells from gaining a foothold. It is known that agents given arterially into the tumor bed have a greater effect on the tumor cells than agents given intra-

venously. This fact has led to the use of these agents by catheter into the arterial supply of the tumor.

More recently, Creech has maintained a tumor-bearing region on extracorporeal circulation during perfusion with chemical agents in high concentration. The ease with which the blood supply to an extremity can be isolated from the general circulation early in the procedure has suggested the use of high dosages of anticancer drugs into the arterial supply of the extremity with the venous drainage blocked. It is hoped that, in addition to the blockage of the main venous return, any tumor cells entering the circulation via accessory veins will have been rendered nonviable. Because this procedure causes little if any depression of the general hematopoietic system, it becomes possible to follow with additional chemotherapy postoperatively.

The 7 cases in which adjuvant arterial chemotherapy was used are summarized in Table III.

It would appear from these studies that large doses of chemotherapeutic agents may be given intra-arterially into the extremity early in the procedure without compromising wound healing and with protection of the hematopoietic system. Further courses may then be given postoperatively as has been done in cancer of other areas such as bowel and breast. This concept of surgery plus arterial chemotherapy will have increased usefulness when more effective chemicals become available.

Rehabilitation. Rehabilitation of the patient must begin when operation is first discussed and must include both him and his family. Preoperative preparation should include training and practice in the use of crutches for hemipelvectomy patients. The patient was out of bed the first postoperative day and was encouraged to use crutches as soon as his general condition permitted which was usually in the range of the second to fifth postoperative day. Exercises under the supervision of the physiotherapy department were begun immediately postoperatively for all patients. After discharge from the hospital, those patients suitable for and desiring prostheses were referred for fitting and training in their use. In general, this was not encouraged except in the younger, more physically fit patient. Fitting of the prosthesis was delayed 6 months to allow further evaluation of the patient for possible metastases. Of the 11 patients who underwent forequarter amputations, 2 men have been fitted with a functioning prosthesis. One man became proficient in its use. The other patient thought that it was too cumbersome to be practical and now uses only a fitted leather and sponge rubber shoulder pad for cosmetic reasons. One other patient, a female, also uses a shoulder pad. Of the 9 patients who had hemipelvectomy only 2, both younger men, have used a prosthesis. One patient with strong motivation and determination became proficient in its use, the other has developed metastases during his training period.

CONCLUSION

Quarterectomy is a practical and successful surgical approach to the removal of selected malignant tumors of the extremities. It is technically possible to combine local arterial chemotherapy with the surgery. Twenty cases, 7 with supplemental arterial chemotherapy, are presented. No conclusions can be drawn as to long range results but further studies are believed to be warranted.

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THE USE OF INTRAVASCULAR BALLOON CATHETERS FOR ISOLATION OF THE PELVIC VASCULAR BED DURING PUMP-OXYGENATOR PERFUSION OF CANCER CHEMOTHERAPEUTIC AGENTS

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In 1958, Creech first described a technique for the regional perfusion of far advanced cancer with chemotherapeutic agents. The circulation to the involved body region was isolated and perfused with a pump-oxygenator. High doses of a chemotherapeutic agent could be administered to the region. Leakage of the chemotherapeutic agent to produce toxic effects in the systemic circuit was minimized by the regional vascular separation.

Application of this technique to a lesion of an extremity gives excellent isolation of the perfused area since tourniquets can be applied at the base of the extremity to prevent exchange of blood through collateral channels. Other regions of the body, such as the pelvis, present additional problems. The collateral circulation cannot be isolated easily and extensive operative procedures are necessary to obstruct the aorta and vena cava to limit the region of perfusion. Our interest has centered upon the perfusion of the pelvic region because of the frequent occurrence of extensive cancer in this region unsuitable for extensive radical surgical procedures or roentgen treatment.

After biopsy, clinical examination in many instances indicates that laparotomy is not necessary to establish the unsuitability of lesions for extirpative surgery. These indications include the presence of obvious fixation or local bone spread with associated involvement of the lower ureters and hydronephrosis. Under these circumstances, the performance of laparotomy solely for the purpose of blocking the aorta and vena cava is a major undertaking likely to be complicated because of the underlying debilitation of such a patient or because of the possibility that the region to be clamped above the bifurcation of the vena cava and aorta might be so extensively involved with tumor tissue that successful dissection of the vessels would be impossible. Such a formidable procedure should be avoided in view of the palliative nature of tumor perfusions. To minimize the operative procedure we have investigated the possibility of using balloon catheters to achieve vessel blockage.

In the laboratory, we first demonstrated that balloon cardiac catheters of the Dotter-Lukas type could be introduced into the groin vessels and passed centrally to produce as satisfactory an obstruction of the aorta and vena cava above the bifurcation as could be obtained by the application of clamps to these vessels (Fig. 1). The catheters were originally designed for pulmonary angiographic studies and present surfaces suitable for intravascular placement. They are radiopaque. They are stiff enough so that there is no bending when the balloon is inflated against the aortic stream and yet are

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pliable enough so that they may be manipulated within vessels as easily as may the conventional cardiac catheter. The catheters have extra lumina which open above and below the balloon to permit monitoring of pressures, the injection of chemical agents, or the withdrawal of blood samples either above or below the point of obstruction (Fig. 2). The following technique has been evolved during clinical application in 6 patients.

TECHNIQUE

Isolation of the pelvic viscera with balloon catheters. The patient is placed supine on an operating table bearing a cassette tunnel to permit exposure of roentgenograms of the umbilical region of the abdominal cavity. After the induction of general anesthesia, the brachial artery is cannulated for purposes of blood sampling, and the necessary balloon catheters and perfusion cannulas are inserted in the femoral vessels through incisions in each groin. Adequate amounts of bone marrow are aspirated both for immediate postoperative reinfusion and for glycerol preservation to permit a second late reinfusion.

Prior to introduction, each catheter is laid out on the anterior abdominal wall taking the approximate course it would in the iliac system with the balloon tip just above the umbilicus. The segment of the catheter at the level of the proposed femoral vessel incision is marked with a ligature. This marker serves to indicate approximately the length of catheter to be introduced—with the ligature at the incision the balloon tip within the vessel should lie just above the iliac bifurcation.

The position of the balloon catheters is confirmed by roentgenograms of the abdomen taken by a portable machine. The venous balloon catheter is introduced through the left saphenous bulb. The arterial catheter is introduced through a major perforating branch of the right femoral artery. By introducing the venous catheter on the left and the arterial catheter on the right, the

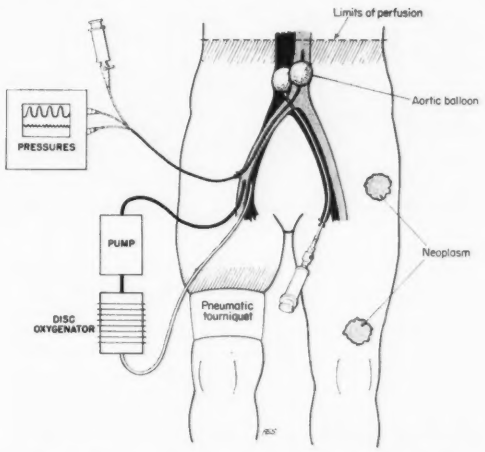

FIG. 1. Diagram of pelvic perfusion technique. Balloon catheters have been inserted to the level of the aortic and caval bifurcation. The pelvic circuit has been connected to the pump-oxygenator through groin cannulas. Pressures above and beyond the point of aortic obstruction are measured with strain gage transducers. A pneumatic tourniquet has been applied to the right leg to prevent passage of mustard to the femur and tibia. In this instance the left leg will be perfused because of the presence of a metastatic neoplastic lesion in the left femur.

crossover point of the catheters as observed roentgenologically may be anticipated to be approximately at the bifurcation of the aorta and vena cava. Final adjustment of position is made so that the balloons lie 2 to 3 centimeters above the crossover point. Radiopaque dyes may be injected to confirm localization of the catheters. On inflation of the arterial balloon in the correct

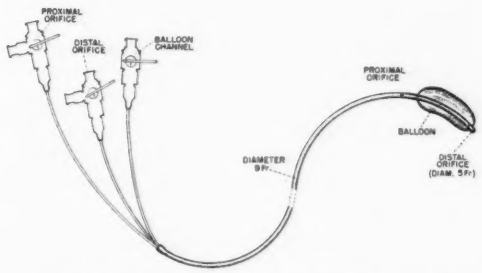

FIG. 2. Vascular balloon catheter of the Dotter-Lukas type. The balloon is inflated with saline solution. Stopcocks are connected to two channels, permitting pressure measurement above and below the point of balloon obstruction, and to one channel used to inflate the balloon.

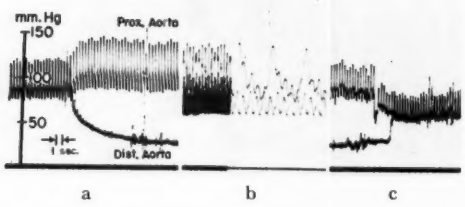

FIG. 3. Strain gage pressure recordings during the course of pelvic perfusion. a, On inflation of the balloon, arterial pressure rises in the proximal aorta but falls to a static pressure of 20 millimeters of mercury in the distal aorta beyond the point of balloon obstruction. Movement artifacts are observed in the distal aortic pressure tracing but no pulses can be seen. b, With the pump-oxygenator perfusing the pelvic circuit, a characteristic pump pressure tracing may be seen. In this tracing an artifact causes transmission of the pulse wave into the proximal aortic tracing but isotope dilution curves indicate adequate isolation. The pressure within the pump circuit is maintained somewhat lower than the pressure within the systemic arterial tree to minimize leakage of chemotherapeutic agents out of the pump circuit. c, After 1 hour of perfusion the pump-oxygenator is stopped and the persisting evidence of adequate aortic obstruction indicated by the fall of distal aortic pressure to the static 20 millimeter level. On release of the balloon catheters the pressure is equalized.

position, pulses should disappear from each femoral artery. On inflation of the venous balloon, venous pressure should rise equally in each femoral vein.

A Luer-Loc stopcock is connected to each channel of the balloon catheter. Each stopcock is greased with silicone grease immediately before insertion in the system. The adequacy of balloon inflation is tested with air for 10 minutes immediately prior to introduction.

Channels in the arterial catheter are connected to strain gage transducers to record arterial pressure above and below the point of balloon obstruction. Similar channels in the venous catheters are used to sample serially venous blood draining the perfused area for isotope mixing curves.

Pressure recording technique. When the balloon in the aorta is inflated to the point of complete obstruction characteristic alterations are observed in the pressure tracing (Fig. 3a). There is a moderate rise in aortic pressure proximal to the point of obstruction and a decline of distal intravascular pressure to a level on the order of 20 millimeters of mercury, with elimination of pulsations. If obstruction of the aorta has been correct, this 20 millimeter pressure level is maintained over the course of a minute or two, and no pulse may be palpated in either exposed femoral artery (Fig. 3).

After such a demonstration of adequate isolation of the vascular bed from the general circulation, perfusion of this area by means of the pump-oxygenator is started, as described previously (5). Since the pumps of the machine have a characteristic pressure pulsation pattern differing from aortic systolic pulsation, a continual observation of the pump circuit pressure pulse pattern on the recording oscilloscope serves to indicate the persisting adequacy of vascular isolation by the balloons (Fig. 4) by showing the absence of aortic systolic pulsation. If there is any question as to the possibility of leakage about the balloon, the pump may be stopped and confirmation of the return of distal vascular pressure to the 20 millimeter mercury level may be made.

Until recently, pneumatic tourniquets had been applied to the thighs below the groin incisions to prevent passage of alkylating agent to the limbs during perfusion of the pelvis. These were inflated to a pressure above arterial pressure prior to the onset of perfusion. A recent instance of renal suppression suggesting crush syndrome has caused us to question the value of such tourniquets.

When the adequacy of isolation of the peripheral circuit is confirmed and stable perfusion through the heart-lung machine is established, a standard number of counts of radioiodine albumin is injected into the pump circuit, and serial sampling of brachial arterial and venous blood draining the perfused segment is carried out (Fig. 5).

During this period of sampling, the desired quantity of freshly prepared nitrogen mustard is injected. Dosage of nitrogen mustard has varied from 0.6 to 1.0 milligram per kilogram of total body weight. The alkylat-

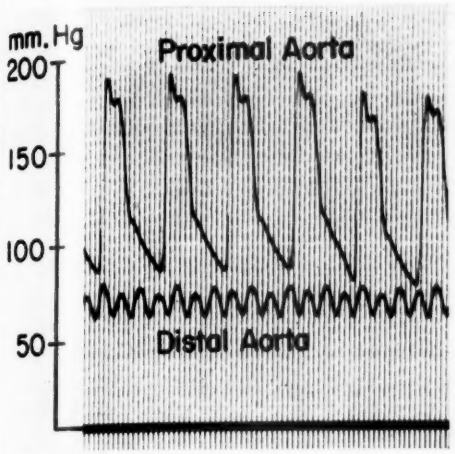

FIG. 4. Characteristic pressure pulses during perfusion. The disparity between the aortic pressure above the point of obstruction in the proximal aorta and the characteristic pump pulse contours without imposition of cardiac pulsations in the distal aorta indicates the adequacy of blockage by the balloon.

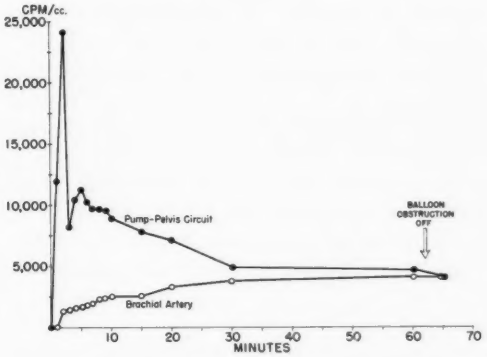

FIG. 5. Disparity between pump circuit tracer concentrations and systemic circulation tracer concentrations within the brachial artery. There is considerable disparity between the concentration of tracer in the brachial artery and pump pelvis circuit during the first 5 minutes following injection, when substances such as the short-acting alkylating agent, nitrogen mustard, are present within the circulation. There is gradual equilibration of tracer concentrations over the course of 30 minutes and complete equilibration after relief of the balloon obstruction.

ing agent is given in 12 divided doses at 5 minute intervals.

Five minutes after injection of the last aliquot of nitrogen mustard, perfusion in the isolated segment is stopped, the competency of the balloon obstruction is confirmed by observation of pressure pulse contours, and a maximal amount of venous blood is drained into the oxygenator—on the order of 500 to 1,000 milliliters of blood—by releasing the aortic balloon obstruction without release of the caval obstructing balloon.

The catheters are then withdrawn and the vascular incisions repaired. If minor branches have been used to introduce the balloon catheters, these vessels may be ligated.

DISCUSSION

We have had sufficient experience in the clinical application of this technique in 6 patients to permit an assessment of the technique under operating room conditions. Laboratory studies have been conducted to evaluate application of the technique in other regions of the body. Mixing curves have been analyzed which indicate that obstruction is reliable and as adequate as the application of clamps but without the necessity for the formidable operation required to apply clamps to the major vessels. Both in the laboratory and in the operating room, the balloons have proved sturdy. Although each catheter is used only once for a clinical perfusion, we have had occasion to use a single balloon catheter for 5 and 8 three hour perfusions in animals and have found that the balloons are rugged enough to withstand this prolonged period of usage without any instance of balloon rupture.

The pattern illustrated in Figure 5, showing a rapid decline in concentration of a tracer agent in the pump circuit and a gradual rise in concentration of isotope in the general circulation, is believed to be the result of mixing through collateral channels. In view of the numerous collateral channels which exist between the pelvic vasculature and the general circulation unavailable even for direct surgical blockage, it is difficult to visualize how operative isolation of the pelvic circulation would achieve better mixing curves than can be achieved

by this procedure. The presence of considerable mixing from the pelvic circuit, however, does limit the use of chemotherapeutic agents to those alkylating agents that rapidly disappear from the circulation during the time the difference between pelvic concentration and general systemic concentration would be expected to be high on the basis of isotope dilution curves. Nitrogen mustard is known to fulfill these requirements. The dosage of the agent to be used has been determined by such preoperative considerations as the status of the bone marrow, the status of the skin in the region to be perfused, and the clinical evidences suggesting that collateral circulation, enhancing mixing, might be increased as a result of obstruction of major vascular channels by the tumor. Two of the first 3 patients demonstrated evidences of mild bone marrow suppression when given a dosage of nitrogen mustard on the order of 2½ times the usual total body dose. Death in a third patient is ascribed to a fulminating bronchial pneumonia, although severe bone marrow depression undoubtedly contributed to the death. At the present time, we would prefer to reduce the dose of nitrogen mustard for such a patient in view of the preoperative findings of bone marrow depression and evidences of debility based upon prolonged intestinal obstruction. Recently, autologous bone marrow has been withdrawn prior to infusion. A portion of this marrow has been reinfused immediately after operation and another portion glycerolized and frozen for possible late infusion. In 2 patients treated in this manner, peripheral blood counts have been maintained satisfactorily.

The time of perfusion has been set arbitrarily at 1 hour although it would be desirable to continue perfusions for longer periods of time in the hope that treatment with alkylating agent would affect more mitotic divisions within the tumor mass. The minimization of the operative procedure necessary in the balloon technique makes such prolongation of the period of perfusion possible.

SUMMARY

A technique is described of isolating the pelvic viscera from the general circulation by the use of balloon catheters of the Dotter-Lukas type. The method has the advantages of minimization of operative trauma to the patient and permits obstruction of major vascular channels, although these channels may be surrounded by tumor.

Precautions are utilized to insure correct placement of the balloons without laparotomy: (1) the position of the catheters is confirmed by roentgenography at the time of operation; (2) the pressures prevailing within the arterial system are continuously monitored above and below the point of obstruction during the course of the perfusion, and (3) dilution curves using radioiodine albumin are carried out to document the persisting evidence of isolation during the course of the procedure.

The use of balloons has proved reliable in a limited clinical and laboratory experience. Mixing of agent between the perfused circuit and the general circulation has occurred as a result of the inability to block collateral channels.

It is not apparent that a better isolation of the pelvic circuit can be obtained by direct operative clamping than by the use of the catheter technique.

The presence of extensive mixing between the pelvic and systemic circuits limits us to the use of short-acting alkylating agents such as nitrogen mustard. The technique offers promise of use in other regions of the body.

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THE POSSIBLE INDICATION OF POSTOPERATIVE THROMBOEMBOLISM BY PLATELET COUNTS AND BLOOD COAGULATION STUDIES IN THE PATIENT UNDERGOING EXTENSIVE SURGERY

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A STUDY WAS MADE to determine whether a period could be found, in patients undergoing extensive surgery, when significant alterations occurred in blood coagulation and total circulating platelets, which could fix a possible time of thrombus formation, a steadily increasing, often fatal surgical complication. The study suggested itself after the earlier observation (6) that surgical thromboembolism, as noted at autopsy, occurred most frequently from the day of operation to the eighth postoperative day. It was assumed from this earlier material that thrombosis, venous or arterial, could develop preceding, during, or after operation and give rise to pulmonary embolism or coronary, cerebral, and mesenteric artery thrombosis. Since these arterial thromboses were observed to occur occasionally in the absence of arteriosclerosis (5), it was believed possible that some alteration of blood coagulation could alone explain this phenomenon in these patients. According to de Takats, a review of previous studies by Bergquist on blood coagulation in the surgical patient, generally conflicting and inconclusive, reveals that the studies were made chiefly after operation and in some instances before.

In the present study, blood coagulation determinations and platelet counts were made during the entire course of the patient's surgical hospitalization, especially on the day of operation. The latter period was chosen for more intensive scrutiny, since this was the day when the earliest thromboembolic episodes had been observed and the time judged to be the period of probably greatest stress. In addition, since Adams noted a distinct blood platelet increase in the postoperative period and Sharnoff and Kim (8) observed an increased pulmonary megakaryocytosis, associated with deaths from thromboembolic disease in general and in postoperative thromboembolism in particular, it was believed possible that the source of the platelet increase was the breakup of the increased number of megakaryocytes into platelets in the pulmonary capillary bed during the surgical stress. Under experimental stress conditions, rabbits have been shown to respond with a significant increase in circulating platelets (9). It also seemed possible that there existed in these surgical patients a relationship between the thrombocytosis and the greater clotting tendency of the blood. This study also served the purpose of determining whether such a relationship could be demonstrated.

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MATERIAL AND METHODS

Forty-one unselected patients undergoing extensive surgical procedures were studied. In 15 patients, blood coagulation times and platelet counts were determined before anesthesia, during operation, on emerging from anesthesia, and then daily until discharge or

FIG. 1. Opened right ventricle seen from its ventral surface shows partly uncoiled 35 centimeter long embolus.

death, but when possible for a minimum of 8 days. In 26 patients similar determinations were made before, during, and after operation on the operative day and a final set of determinations on the day of discharge. In 3 instances the studies were terminated abruptly with the sudden deaths of these patients. Autopsy was performed on 2 of the 3 and disclosed that 1 death was due to a massive pulmonary embolism (Fig. 1) on the second postoperative day and the second to coronary thrombosis and acute myocardial infarction on the twelfth postoperative day. The third patient died suddenly with classical clinical signs of pulmonary artery embolism on the fifth postoperative day. These 3 patients will be presented hereinafter in greater detail.

Coagulation times were obtained by the method of Lee and White; platelet counts in duplicate, by the indirect method of Fonio. The latter was modified only in that the blood was collected in versene, the disodium salt of ethylene dinitrotetra-acetic acid, thus obviating the use of magnesium sulfate. This modification proved to be extremely satisfactory as manifested by the reproducibility of the results and especially the closeness of the paired counts. Erythrocyte counts were determined by the counting chamber method. The patients studied were predominantly adults ranging in age from 16 to 83 years. All types of operations, chiefly abdominal surgery, were performed on these individuals. The length of the surgical procedure varied from approximately 30 minutes to 3 hours. The anesthetic used was either general or spinal. General anesthesia consisted of induction with sodium pentothal followed by cyclopropane and ether. Spinal anesthesia was used in 11; a general anesthetic in the other 30 cases.

RESULTS

A striking alteration of coagulation times and platelet counts were noted in almost all instances, especially during operation or immediately after the operative period on the operative day. In several instances, a secondary similar effect was observed on the first to fifth postoperative days. The blood changes observed were a significant temporary shortening of blood coagulation time with a concomitant significant temporary rise in circulating platelets. The coagulation times often fell below the normal lower limit of 5 minutes before returning to normal preoperative levels. The platelet counts rose abruptly with the fall in coagulation times and returned shortly to preoperative levels and often showed a later moderate steady rise.

As can be seen in Figure 2 of the group of 15 patients, the sharpest average fall in coagulation times was recorded during operation, the averaged times going from 6 minutes and 50 seconds preoperatively to 4 minutes and 52 seconds during operation, indicating a 28.8 per cent fall. At the same time there was noted the sharpest and most abrupt average increase in the number of platelets from 233,000 to 305,000 per cubic millimeter, representing a 30.9 per cent

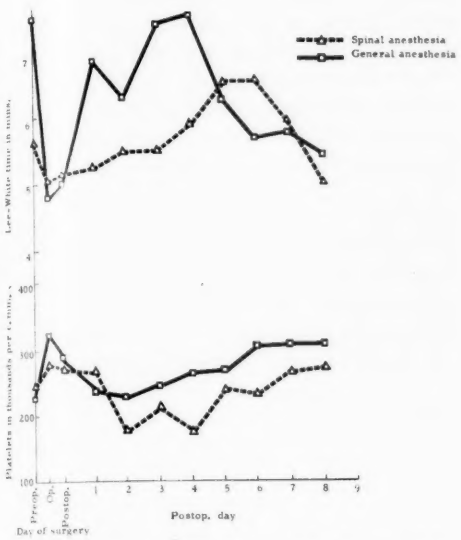

FIG. 2. Averaged values of Lee and White coagulation times and platelet counts of 15 patients followed up during entire surgical course.

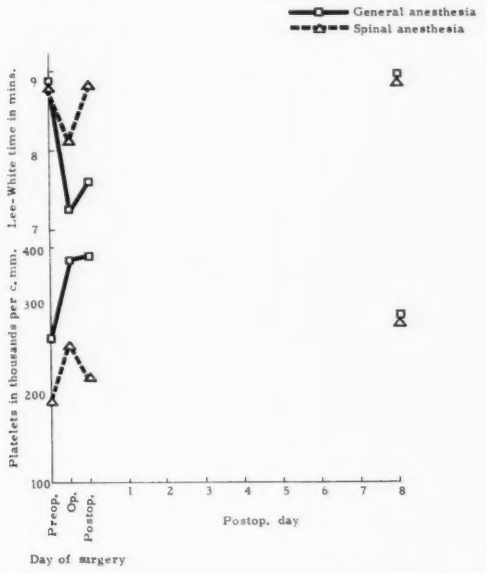

FIG. 3. Averaged values of Lee and White coagulation times and platelet counts of 26 patients on day of operation and similar determinations on the day of discharge.

rise. In 5 patients in this group, under spinal anesthesia, there was revealed a strikingly smaller fluctuation in these values compared to the values obtained in patients under general anesthesia. Thus, an 11.1 per cent fall in average coagulation time and a 10.9 per cent increase in the average of platelet counts is recorded in those individuals given a spinal anesthetic compared to a 35.2 per cent fall in average coagulation times and a 43.5 per cent average increase in platelets in those given a general anesthetic.

Similar values were obtained in the larger group of 26 individuals studied on the day of operation (Fig. 3). Here again, the values obtained in the operative period are most striking. The total average fall in coagulation times was from 8 minutes and 40 seconds preoperatively to 7 minutes and 27 seconds during operation, representing a 14.0 per cent decline, while the average number of platelets rose from 266,000 to 342,000 per cubic millimeter, indicating a 21.0 per cent increase. A difference was noted, as before, between patients operated upon under spinal anesthesia compared to those in whom a general anesthetic was used. In 6 individuals under spinal anesthesia the average coagulation times fell 6.6 per cent and average number of platelets rose 41.8 per cent. The 20 patients under general anesthesia, however, revealed a fall in coagulation time from an average of 8 minutes and 41 seconds to 7 minutes and 18 seconds, representing a decline of 15.7 per cent, and a rise in average platelets from 284,000 to 357,000 per cubic millimeter, representing a 28.5 per cent increase.

In the 2 instances which terminated in postoperative death and revealed thromboembolism at autopsy as the cause of death, the values recorded are more striking. The first patient, a 58 year old white female undergoing a 1 hour and 30 minute intestinal resection for cecal carcinoma was given a spinal anesthetic and sodium pentothal. During the operation she was transfused with 500 cubic centimeters of blood. Her blood pressure dropped slightly during the operation and then rose to the preoperative

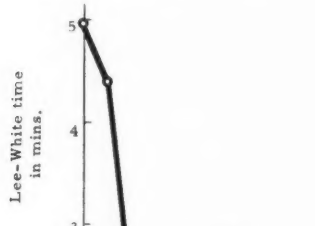

FIG. 4. Lee and White coagulation times and platelet counts in the patient who died of massive pulmonary embolism (Fig. 1).

level of 140 systolic and 75 diastolic. Her pulse rate dropped from 90 per minute to 70 per minute during the operation. Postoperatively, the patient made a rapid recovery and then suddenly died in respiratory difficulty on the second postoperative day. Autopsy disclosed the massive pulmonary embolism referred to previously (Fig. 1). The embolus measured 35.0 centimeters in length, and from its size and configuration it may be assumed that it arose from the leg veins. The greatest percentage fall in coagulation time (Fig. 4) was observed in this patient. This fall occurred in the immediate postoperative period, 30 minutes after the operation was concluded. In this patient a drop from the preoperative level of 4 minutes and 38 seconds to 2 minutes and 5 seconds took place, corresponding to a 55.0 per cent fall in coagulation time. At the same time there was recorded a 66.0 per cent rise in platelets from 221,000 to 367,000 per cubic millimeter. There followed an immediate return of these values to more normal levels on the following day.

The second patient, a 75 year old colored female also underwent an intestinal resection for carcinoma of the cecum. She was placed under general anesthesia with sodium pentothal, cyclopropane, and ether. There was no alteration of blood pressure or pulse rate. Pulse rate was 85 per minute, and blood pressure was 140 systolic and 100 diastolic. Duration of the operation was 1 hour and 40 minutes. Here again, the values obtained are striking (Fig. 5). Coagulation time fell from 6 minutes and 15 seconds preoperatively to 3 minutes and 39 seconds during operation, representing a 41.7 per cent decline. The greatest rise in platelets was recorded as the patient emerged from anesthesia. The platelets rose from 187,000 per cubic millimeter preoperatively to 418,000 per cubic millimeter in the postoperative period, indicating a 123.0 per cent increase. Postoperatively, the patient was treated for signs of cardiac failure and died on the twelfth postoperative day. Autopsy disclosed an acute myocardial infarction with thrombosis of the descending branch of the left coronary artery. Myocardial infarction was judged to be of approximately 2 weeks' duration.

In 7 other instances, similar marked alterations of the coagulation times and platelet counts were observed. However, in only 1 was a thromboembolic complication observed. This was the third postoperative death referred to earlier in which striking clinical evidence of pulmonary embolism as the cause of sudden death was noted. This patient, a 65 year old white male had a gastric resection for chronic duodenal ulcer. He was given a general anesthetic. The surgical and postoperative course was uneventful. On the fifth postoperative day, on getting out of bed, going to the bathroom, and returning to his bed, he died suddenly in respiratory difficulty. Permission for an autopsy was refused. In this instance, a 47.7 per cent fall in coagulation time was recorded on the second postoperative day,

from 10 minutes and 56 seconds preoperatively to 5 minutes and 43 seconds. At the same time a 48.7 per cent rise in platelets was observed. In the remaining 6 of these 7 instances, a sharp fall in coagulation times and a rise in platelets was observed during the period of operation. The fall in coagulation times ranged from 37.5 to 52.1 per cent, while the rise in platelets ranged from 16.4 to 118.2 per cent. In 4 of the 7 individuals, blood coagulation times below normal levels were observed. The lowest recorded coagulation times were 3 minutes and 22 seconds and 3 minutes and 21 seconds in 2 instances.

DISCUSSION

The blood values obtained clearly indicate that at least 1 and sometimes 2 transient abrupt episodes of marked shortening of blood coagulation times associated in all instances with a transient increase in platelets occur in the patient undergoing extensive surgery. This is observed most frequently during the actual operation. The shortening of blood coagulation time often falls below normal levels and may therefore be designated as blood hypercoagulability. It would appear that this period of blood hypercoagulability may be the most critical and the most likely time for the development of either venous or arterial thrombosis. The venous thrombus may at a later time be dislodged and produce pulmonary embolism with or without infarction and possible death. The arterial thrombus may produce early clinical signs of its occurrence or may immediately or later cause death.

The 3 patients suffering postoperative thromboembolic death also revealed the most marked alterations in blood values. This alteration was observed either as blood hypercoagulability or in the percentage fall of coagulation time. Likewise, the greatest rise in platelets was observed in these individuals. In 6 instances, however, no thromboembolic complications were noted, though the blood values recorded are almost equally as marked as in those in whom thromboembolic death occurred. The blood

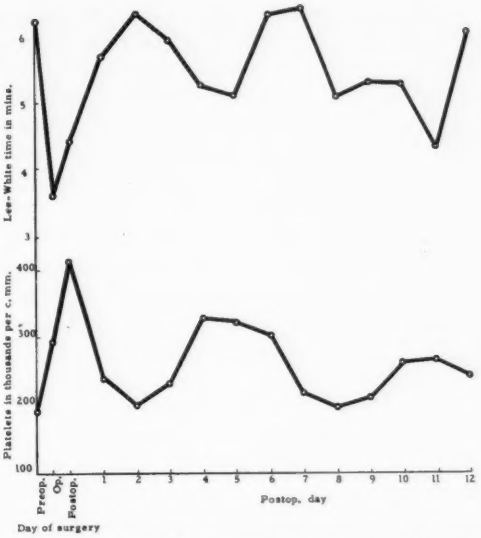

FIG. 5. Lee and White coagulation times and platelet counts in a patient who died of acute coronary thrombosis and acute myocardial infarction.

alterations in the remaining 32 patients, though showing the same general pattern, were not as marked. From these facts it may be concluded that the point at which thrombosis occurs may vary somewhat from one individual to another but that thrombosis is most likely to occur when the change in blood values is most marked. It may also be surmised from these facts that it may require a relatively slight alteration of blood coagulation time in order to prevent thrombosis. Though the study was made on a year round basis, it may or may not be significant that the 3 deaths observed occurred in the winter months of January, February, and March.

In our opinion the associated platelet increase is not necessarily the cause of thromboembolism but is merely a reflection of what transpires in the pulmonary capillary bed of these patients under surgical stress. This phenomenon may be explained in the following concept. In a series of studies (5–9) it has been shown that the pulmonary capillaries may be a significant site of platelet formation from bone megakaryocytes which are normally transported to the lung vessels. The studies have also shown that as a nor-

mal phenomenon 2 to 3 megakaryocytes are usually seen per square centimeter of lung tissue section. Under stress conditions, however, larger numbers of these megakaryocytes may be transported to the lung vessels and under further stress break up more rapidly than under normal circumstances into platelets and thus cause a thrombocyte increase in the peripheral circulation. This increase in the number of pulmonary megakaryocytes, with often as many as 30 to 40 per square centimeter of lung tissue section, was observed in patients after death from hemorrhage from thromboembolic disease, but is seen especially in postoperative deaths. Thus the degree of increase in platelets may depend on the number of megakaryocytes present in the lung vessels during the period of greatest stress. Since the megakaryocytes have also been shown to contain large quantities of polysaccharides in their cell cytoplasm it may be assumed that in the breaking up of the megakaryocytes their polysaccharides are released into the blood, increasing their concentration there. Rosenlund has noted that experimentally stressed animals have shown an increase of hexoseamines in the blood. Thus the marked increase in platelets may reflect the breaking up of a large number of megakaryocytes in the lung capillary bed, thereby adding larger quantities of polysaccharides as possible coagulating substances to the blood. This increase, in turn, may be the cause of blood hypercoagulability.

CONCLUSIONS

It would appear that the stress of extensive surgery may be the stimulating factor productive of blood hypercoagulability and its associated thrombocytosis. These blood alterations are observed chiefly during or occasionally immediately after operation. They may also occasionally occur in the first 5 postoperative days. It is most probable that thrombosis occurs at the time of greatest blood hypercoagulability and may be venous or arterial.

The blood hypercoagulability and platelet increase are not influenced by the type or duration of operation nor by the age of the patient. Spinal anesthesia compared to general anesthesia does, however, produce less marked blood alterations in most instances. Yet severe alterations in blood values may be observed in a few individuals given a spinal anesthetic, indicating that this form of anesthesia will not entirely prevent thromboembolism.

If the explanation of the development of blood hypercoagulability and its associated thrombocytosis from pulmonary megakaryocytes as herein offered is valid, anticoagulation appears to be the only potential means of counteracting this phenomenon. This conclusion is based on the assumption that the presence of pulmonary megakaryocytosis cannot be prevented. From observations made in this study, preventive anticoagulation would need to be instituted preoperatively, maintained during operation, and continued for the greater part of the postoperative period. Our observations tend to indicate that only a small degree of anticoagulation may suffice to prevent thromboembolism. The degree and type of anticoagulation that may be effective can be determined only by a thorough trial study.

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SUCCESSFUL USE OF TEFLON GRAFTS FOR SUPERIOR VENA CAVAL REPLACEMENT

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THE CLINICAL IMPORTANCE of obtaining a suitable means of superior vena caval replacement has been discussed in detail in previous communications from this laboratory (5, 7–9). Of the free grafts employed, only fresh segments of autogenous aorta have proved to be consistently successful in caval replacement (5). The graft of autogenous aorta was obtained by replacing the resected segment of proximal descending thoracic aorta with an alcohol preserved aortic homograft through a left thoracotomy. The animal then was turned and superior vena caval replacement was carried out through a high right thoracotomy. The magnitude of such an undertaking has limited the clinical applicability of this means of caval replacement.

Accordingly, the present study was carried out to investigate the suitability of a more practical method of caval replacement utilizing synthetic crimped vascular prostheses made of teflon. The synthetic character of the grafts has made it possible, in addition, to investigate the suitability of grafts of varying known size in animals of relatively standard size. Crimped teflon grafts ranging from 5/16 to 12/16 inch in diameter were employed for superior vena caval replacement in 78 dogs.

MATERIAL AND METHODS

Healthy mongrel dogs were used. The weight of the dogs ranged from 8 to 12 kilograms. Intravenous pentothal was utilized for anesthesia. Oxygen was administered through an endotracheal tube by means of a mechanical respirator. A right third intercostal space thoracotomy incision was employed.

When the right side of the chest was opened, the superior vena cava was dissected free from surrounding structures. The pericardium was opened in the area of the entrance of the superior vena cava into the right atrium. A Potts coarctation clamp was placed across the right atrium caudad to the entrance of the superior vena cava, and a Glover vascular clamp was employed to occlude the superior vena cava and its major branches just cephalad to the origin of these branches. A segment of superior vena cava, ranging from 2 to 3 centimeters in length, was resected between the occluding clamps. The resected segment of vena cava was replaced with a preclotted vascular graft of crimped teflon, of the Edwards-Tapp type. Five sizes of graft were employed. The diameters of the grafts were 5/16, 3/8, 1/2, 5/8, and 3/4 inch The smaller grafts tended to be significantly smaller in diameter than the replaced segment of vena cava, and the larger ones were considerably larger. The 1/2 inch grafts were made of woven teflon and were relatively pliable. Nearly all of the remaining grafts were made of knitted teflon and were relatively rigid. A continuous over-and-over suture of No. 6-0 arterial silk was employed for all anastomoses. Bleeding at the suture line after completion of the anastomoses and release of the occluding clamps seldom was a problem, and additional sutures rarely were required. In this low pressure system, no difference

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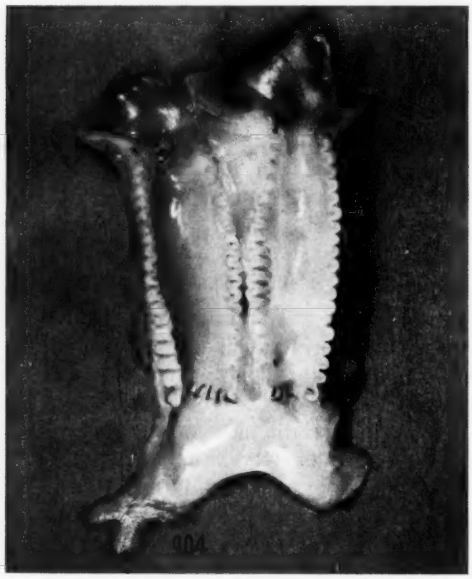

FIG. 1. Photograph illustrating the adequate lumen of the opened 5/16 inch graft in dog 904 at sacrifice 99 days after operation.

was noted between the woven and knitted grafts after preclotting. No effort was made to cover the teflon graft with surrounding pleura. In the majority of the animals the azygos vein was ligated after restoration of caval circulation. The thoracotomy incision was closed in layers, and a catheter which was left in the chest during closure was aspirated and withdrawn.

RESULTS

Superior vena caval replacement with crimped teflon vascular grafts was carried out as described in 78 animals. The patency of the grafts was evaluated by cavogram, postmortem examination, or both from 2 to 413 days after operation.

The 5/16 inch in diameter grafts were the smallest studied. These grafts were significantly smaller than the replaced segment of superior vena cava. All were made of knitted teflon and were relatively rigid. Five-sixteenths inch grafts were used in 12 animals. From 1 to 3 cavograms were obtained in 6 animals, and autopsy study of the grafts was carried out in 10 animals. Four animals died and 6 were sacrificed. Eight of the 12 grafts (67 per cent) were found to be patent. The patency of 7 of the grafts was investigated in excess of 3 months after operation. All of the patent grafts studied at postmortem examination were found to have an adequate lumen (Fig. 1). Stenosis of the lumen was not found in this group of animals. One animal is living. A recent cavogram in this animal, nearly 14 months after operation, has shown the graft to be patent. The cavogram appearance of the graft in this animal 14 months after operation is identical to that observed on roentgenographic study 1 and 4 months after operation.

The 3/8 inch in diameter grafts were slightly smaller than the replaced segment of superior vena cava in the majority of animals, and were made of relatively rigid, knitted teflon. These grafts were employed in 20 animals and 13 (65 per cent) were patent at the time of autopsy or the most recent cavogram evaluation. The cavograms in 13 animals were studied. Postmortem examination was carried out in 19 of the animals from 2 to 351 days after operation. Twelve animals died and 7 were sacrificed. All but 1 of the patent grafts were found to have a satisfactory lumen. The lumen of the graft in this 1 animal was found to be narrowed because of a local area of stenosis. This animal died 12 days after operation. Thirteen of the animals in this group were studied by one or more cavograms from 14 to 159 days after operation. The cavogram in another dog, 14 days after operation, showed the graft to be patent but with some stenosis in the area of the proximal suture line. When this animal died 33 days after operation, the graft was found to be completely occluded by thrombus formation. This was the only instance in the entire series in which initial graft patency by cavogram was followed by subsequent graft occlusion. It is of interest that the graft remained patent in all of the last 10 animals operated upon in this group.

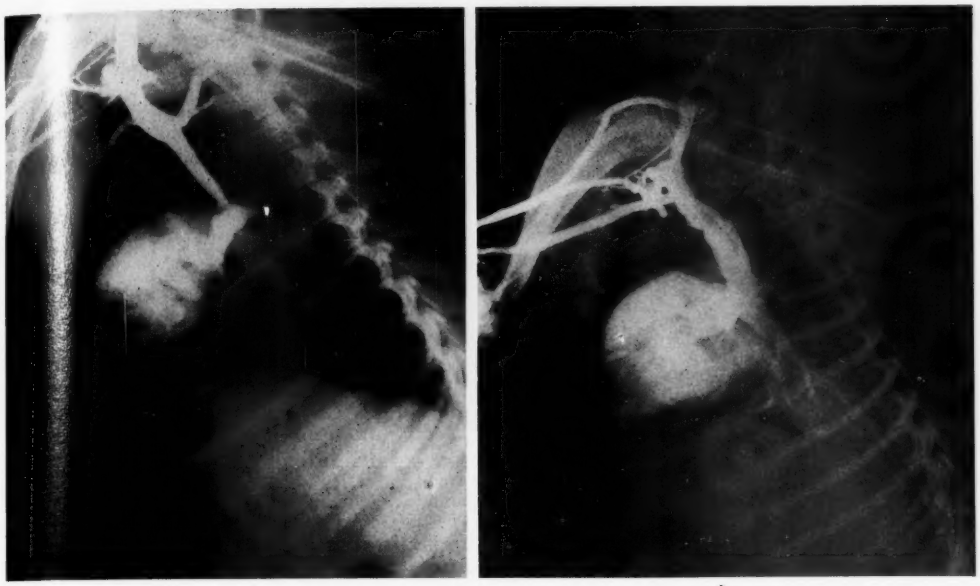

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FIG. 2. Cavograms illustrating the relationship of the size of the teflon graft (arrows) to that of the replaced superior vena caval segment. a, Cavogram of a 5/16 inch graft in dog 803, 35 days after operation. This graft is smaller than the replaced caval segment. b, Cavogram is of a ½ inch graft in dog 643, 28 days after operation. The graft is slightly larger than the replaced caval segment. It was patent on sacrifice 236 days after operation. The postmortem appearance of this graft is shown in Figure 6.

The ½ inch in diameter grafts were slightly larger than the replaced caval segment (Fig. 2). All of these grafts were made of woven teflon and were less rigid than the other sizes of grafts employed in this study. At times, some mild buckling of the graft at the anastomotic suture lines was observed due to this relative pliability and the greater diameter of the graft than that of the replaced caval segment. Half inch grafts were employed in 26 animals and 18, 69 per cent, remained patent. Graft patency was studied by 1 or 2 cavograms in 20 animals and at postmortem examination in 21 animals. Of the animals studied at postmortem examination, 11 died and 10 were sacrificed. The periods of observation in this group ranged from 2 to 236 days after operation. Thirteen animals were studied in excess of 5 months after operation and the grafts in all were found to be patent. Five of these animals are being kept alive for long term observations. A satisfactory graft lumen was encountered in 12 of the 13 patent grafts studied at autopsy. One animal was found by cavogram 14 days after operation, to have some narrowing of the graft lumen, and at sacrifice, 21 days after operation, some stenosis of the graft lumen due to thrombus formation was found. Some suture line fraying of the graft at the time of operation had been recorded in this animal. Sixteen of the last 19 half inch grafts have remained patent.

The ⅝ inch in diameter grafts were significantly larger than the replaced segment of superior vena cava. In some of the animals, enlargement of the lumen of the vena cava by one or two linear incisions was necessary to complete the anastomosis because of the greater size of the lumen of the graft. All but 2 of the grafts were made of relatively rigid knitted teflon. Ten of these

FIG. 3. Cavogram appearance of the ½ inch graft in dog 661, 217 days after operation.

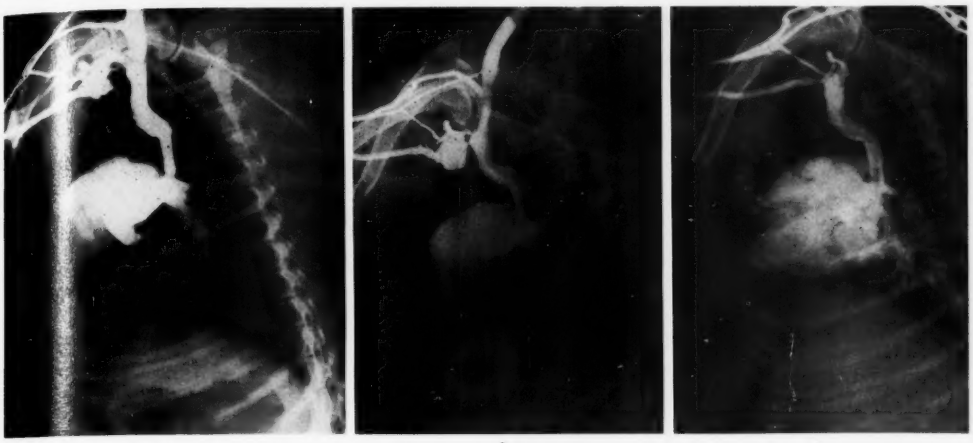
grafts were used for caval replacement and 9, 90 per cent, were found to be patent on examination from 14 to 255 days after operation. One animal was studied by cavogram, and postmortem examination was carried out in all 10. Two animals died and 8 were sacrificed. Some relative narrowing of the graft lumen was encountered at autopsy in 3 of the 9 patent grafts. This narrowing tended to occur at the proximal suture line.

The ¾ inch in diameter grafts were considerably larger than the replaced caval segments. At times, the graft appeared to be nearly twice the size of the superior vena cava. Enlarging incisions in the vena cava at the site of the caval graft anastomoses often were required. All but 1 of these grafts were made of relatively rigid knitted teflon. Ten ¾ inch grafts were employed and 9, 90 per cent, remained patent. The periods of observation ranged from 30 to 280 days. Six grafts were studied by one or more cavograms, and postmortem examination was carried out in 9. Four animals died and 5 were sacrificed. The 1 relatively nonrigid graft was the only graft to become occluded. The graft became flattened at the time of placement because of the great disparity between the sizes of the graft and the vena cava and the pliability of the graft. At autopsy, this graft was found to be flattened and occluded by thrombus formation.

In the total series of 78 animals, the teflon graft was found to be patent in 57 animals, 73 per cent. Seven animals are living and 2 are missing from the colony. Graft patency in these animals was evaluated by cavogram only. Sixty-nine animals are dead. Thirty-three of these died and 36 were sacrificed. Postmortem examination was carried out in all of the dead animals. Thirty-eight of the dead animals also were studied by 1 or more cavograms prior to death.

It is of interest that, in the last 50 consecutive animals operated upon, 43 of the teflon grafts, 86 per cent, remained patent. Analysis of the graft size in these last 50 caval replacements reveals that 7 were of the 5/16 inch size, 11 of the ⅜ inch size, 19 of the ½ inch size, 10 of the 5/8 inch size, and 3 of the ¾ inch size. The greater success in this more recent group of replacements is most likely due to greater experience in the technique of caval replacement with these synthetic vascular prostheses.

The use of cavograms proved to be of value in following up the patency of the grafts (Fig. 3). Forty-seven animals were studied by cavogram. The initial cavogram was carried out from 14 to 35 days after operation in 27 animals, from 40 to 63 days in 16 animals, and from 89 to 105 days in 4 animals. A second cavogram was obtained in 9 animals and a third in 1 (Fig. 4). At the time of the initial cavogram, 38 of the 47 grafts were patent, 81 per cent. One of the animals with a patent graft disappeared from the colony after the initial cavogram. Thirty-seven of the animals in which graft patency was demonstrated on the initial cavogram have been followed up by subsequent cavogram, autopsy, or both. All but 1 of the 37 grafts were shown to have remained patent on subsequent study. In the 1 graft failure following initial cavogram



a b c

FIG. 4. Cavogram appearance of the $\frac{5}{16}$ inch graft (arrows) in dog 802; a, 35 days, b, 117 days, and, c, 413 days after operation, showing satisfactory retention of patency and no essential change in the caliber of the lumen.

patency there was evidence of partial stenosis of the graft on cavogram 14 days after operation. When the animal died 19 days later, the graft was completely occluded by a thrombus. In the 36 patent grafts which retained their patency on subsequent study the interval between the initial cavogram and the last evaluation of patency by cavogram or autopsy ranged from 3 to 8 days in 4 animals, from 40 to 99 days in 7 animals, from 107 to 196 days in 19 animals, and, from 208 to 378 days in 6 animals.

The relative size of the grafts appeared to be a factor in the retention of patency. Grafts larger than the replaced segment of superior vena cava seemed more likely to remain patent than grafts which were smaller than the replaced caval segment. The great majority of the grafts of all sizes, except the $\frac{1}{2}$ inch in diameter grafts, were of the relatively rigid knitted teflon type. The $\frac{1}{2}$ inch grafts all were of the less rigid woven teflon type.

In addition, the relatively rigid grafts appeared more likely to remain patent than the more pliable and compressible ones. One of the 2 failures in the group of 20 grafts which were significantly larger than the replaced caval segment was a less rigid graft which became flattened and subsequently occluded by thrombus formation.

The teflon grafts were tolerated well and tissue reaction was minimal. Gross examination of the patent grafts on postmortem examination showed that the lumens remained widely patent with a relatively thin intimal lining of the graft in most instances (Figs. 5 and 6). Microscopic investigation of the teflon graft confirmed the absence of significant histologic tissue reaction and gave evidence of the relatively thin nature of the lining tissue superficial to the peaks of the crimped graft (Fig. 7).

Three animals were operated upon a second time from 2 to 3 months after graft placement in order to investigate the suitability of the endothelium-lined teflon graft for the replacement of a resected segment of esophagus. In the statistical analysis these animals are considered as having been sacrificed. The teflon graft was excised with relative ease because of the minimal nature of the tissue reaction and was replaced with a second teflon graft with little difficulty. This experience illustrated the relative ease with which an unsuitable teflon graft might be removed and replaced with another more suitable graft.

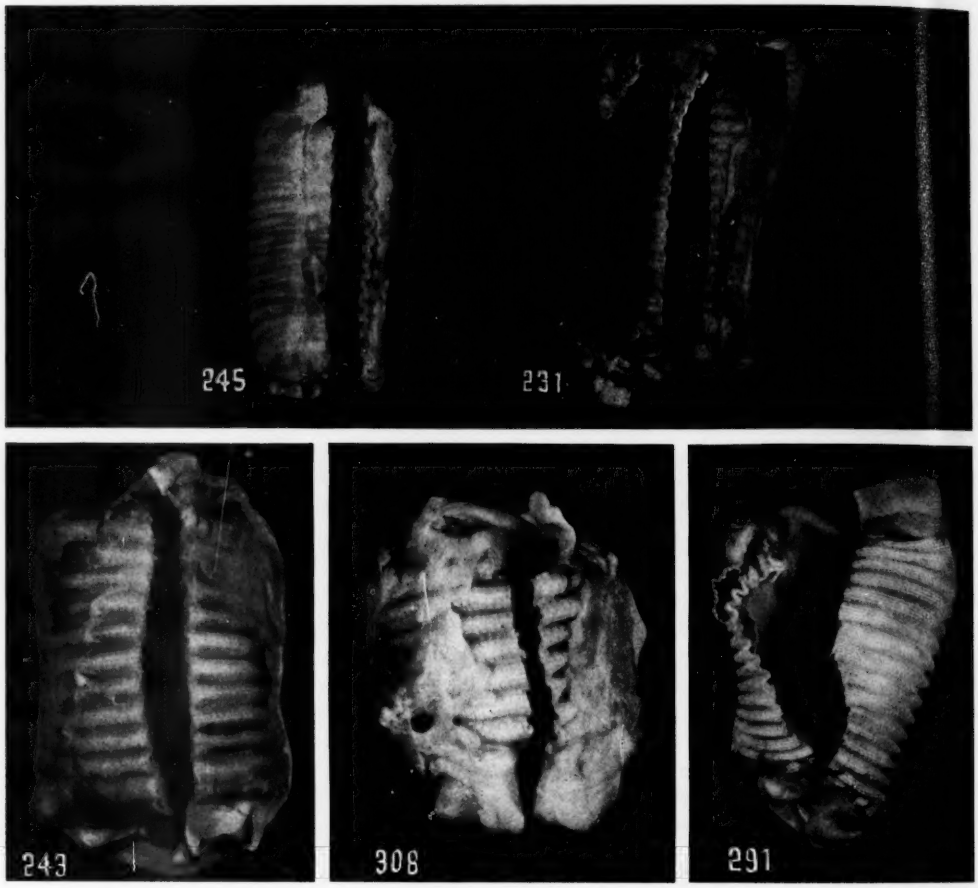


FIG. 5. Photographs showing the postmortem appearance of representative examples of the 5 sizes of graft employed. All were patent and obtained at sacrifice. The 5/16 inch graft in dog 245 was examined at 128 days after operation, the 3/8 inch graft in dog 231 at 139 days, the 1/2 inch graft in dog 243 at 140 days, the 5/8 inch graft in dog 308 at 85 days, and the 3/4 inch graft in dog 291 at 90 days.

DISCUSSION

The results of this study suggest that the superior vena cava of an 8 to 12 kilogram dog may be replaced with a relatively rigid crimped teflon vascular graft which is slightly to moderately larger than the replaced caval segment with an expectation of success in the neighborhood of 90 per cent. The last 50 consecutive caval replacements, employing grafts of all sizes, were carried out with a patency incidence of 86 per cent. This degree of success in the replacement of the superior vena cava of these relatively small animals leads one to speculate that an even greater degree of success with this type of graft might be achieved in the replacement or bypass of the somewhat larger superior vena cava of man. The relatively rigid nature of the graft serves to maintain the lumen of this low pressure vascular channel substitute by preventing its compression by extraneous forces.

The gross and microscopic evidence of minimal tissue reaction to these teflon vascular grafts and the observed ease of their operative removal and replacement indicate further the desirability of a clinical trial of the suitability of relatively rigid teflon grafts for superior vena caval replacement. This apparent success of relatively rigid teflon grafts in superior vena caval replacement may also suggest the possible suitability of teflon for the replacement of other low pressure vascular conduits. Indeed, we have recently observed (6) that 16 of 17 teflon grafts used to replace resected segments of proximal left pulmonary artery remained patent.

Cavograms were useful in assessing the patency of the grafts and in following the continuing patency by repeated roentgenographic studies without the necessity of sacrificing the animal. It was of interest that 36 of 37 grafts which were found to be patent at the time of the initial cavogram remained patent on subsequent roentgenographic or postmortem study. The 1 graft which subsequently became occluded was observed to be partially occluded at the time of the initial postoperative cavogram. This finding suggests that grafts which remain patent during an early critical postoperative period, in all likelihood, may be expected to remain patent.

The importance of employing relatively large and relatively rigid conduits in caval replacement was suggested from experience with the use of comparatively large and rigid alcohol preserved heterografts of bovine aorta for superior vena caval replacement in dogs (9). A surprisingly high percentage of these grafts remained patent.

Experience with the experimental use of synthetic tubes for superior vena caval replacement was reported in 1955 by Deterling and Bhonslay. They employed ivalon tubes, cylinders made from sheets of woven dacron or nylon, and woven seamless tubes of nylon in a total of 16 dogs with disappointing results. The graft became occluded in 9, and significantly obstructed in 4. Only 3 remained patent with good lumens and satisfactory function as demonstrated on cavogram.

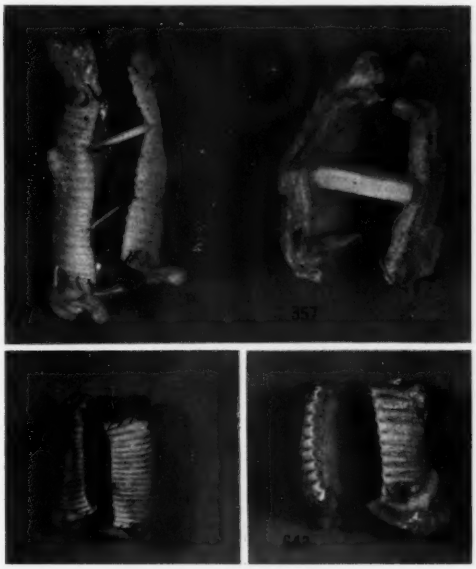
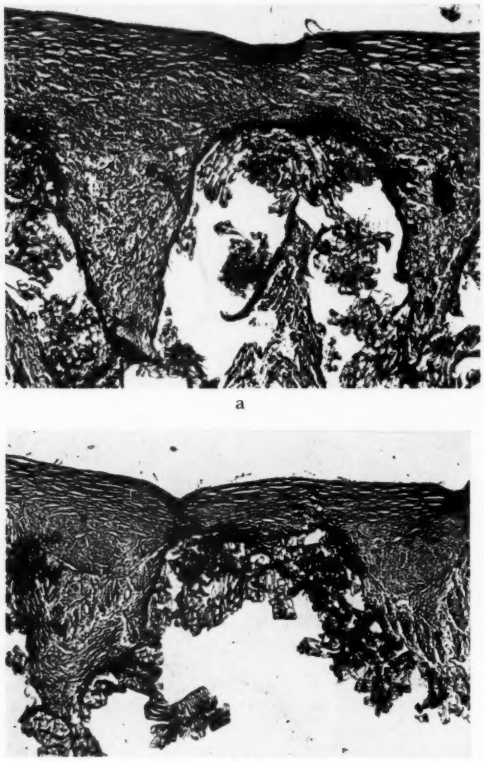


FIG. 6. Photographs of 4 teflon grafts examined at autopsy. All were widely patent and the intimal lining of the grafts was relatively thin. The photomicrographic appearance of the ½ inch grafts from dogs 637 and 357, examined 165 and 197 days after operation, are pictured in Figure 7. The ¾ inch graft from dog 381 was examined 267 days after operation. The ½ inch graft from dog 643 was obtained at sacrifice 236 days after operation and its cavogram appearance 28 days after operation is shown in Figure 2b.

Encouraging short term experience with the use of teflon grafts for superior vena caval replacement in 40 dogs has been reported by the senior author (4). East and Muller, in 1960, recorded their experience with nylon and teflon vascular prostheses for superior vena caval replacement in 14 dogs. One of 7 nylon tubes became occluded and the remaining 6 grafts were found to have varying degrees of lumen constriction. One of the 7 teflon grafts was found to be occluded on postmortem examination, and the other 6 remained patent. Five of the 7 teflon grafts were followed up for 5 weeks or less after operation, and the remaining 2 grafts were studied at autopsy 16 and 24 weeks after operation. In addition, Botham and his



a

b

FIG. 7. Photomicrographs showing the relatively thin intimal lining of the crimped teflon graft from, a, dog 637, 165 days after operation and, b, dog 357, 197 days after operation. The graft has fallen away during sectioning in dog 357. The gross appearance of these grafts may be seen in Figure 6.

associates in 1960 reported the use of tubes constructed from a sheet of porous teflon for superior vena caval replacement in 20 dogs. The patency of the graft was studied from 1 week to 6 months after operation by cavogram or autopsy. Fifteen grafts were patent and 5 were occluded.

SUMMARY

1. The literature pertaining to the experimental use of tubes made of synthetic materials for superior vena caval replacement is reviewed briefly.

2. The use of 5 sizes of crimped teflon grafts for superior vena caval replacement in 78 dogs is reported. Relatively small dogs, weighing from 8 to 12 kilograms, were employed. The grafts ranged from 5/16 to 12/16 inch in diameter. Some of the grafts were smaller and others larger than the replaced caval segment.

3. The patency and functional suitability of the grafts were studied by cavograms, autopsy, or both from 2 to 413 days after operation. Fifty-seven of the 78 grafts, 73 per cent, retained their patency. Forty-three of the last 50 consecutive grafts, including grafts of all sizes, remained patent, 86 per cent.

4. A higher incidence of patency was experienced when the larger grafts were employed. Ninety per cent of 20 grafts of the two largest sizes remained patent, whereas only 65 per cent of 32 grafts of the two smallest sizes remained patent. In addition, a greater degree of success was achieved when the more rigid grafts were used. The more rigid grafts were made of knitted teflon.

5. Cavograms proved to be of value in following up the patency of the grafts. Fifty-seven cavograms were made in 47 animals. Thirty-eight of the 47 grafts were found to be patent at the time of the initial cavogram, 81 per cent. The continuing patency of 37 grafts was evaluated by subsequent cavograms, autopsy, or both, and 36 were found to have retained their patency, 97 per cent. The graft of the 1 failure was found to be partially occluded at the time of the initial cavogram 14 days after operation. This finding suggests that teflon caval grafts which remain patent through an early critical postoperative period may be expected to retain their patency.

6. Gross and microscopic tissue reaction to the teflon grafts was minimal. The intimal lining of the teflon grafts tended to be relatively thin. Because of this minimal tissue reaction, it was found that operative removal and replacement of the teflon grafts could be carried out with relative ease.

7. The results of this study suggest that superior vena caval replacement with rela-

tively rigid crimped teflon vascular grafts, slightly larger than the replaced caval segment, may be carried out with expectation of success in the neighborhood of 90 per cent. Accordingly, a clinical trial of the suitability of teflon grafts for superior vena caval replacement would appear to be worth while.

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SELECTIVE INTRA-ARTERIAL PERFUSION OF TOTAL ABDOMINAL VISCERA FOR CARCINOMA

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IMPROVEMENTS in the equipment and methods for extracorporeal circulation have made it possible to treat patients with anticancer drugs through the intra-arterial route over prolonged periods of time. Recent studies from several clinics have indicated the potential value of this approach and current reports indicate considerable technical success with selective arterial perfusion. During the past 9 months we have attempted an extension of this approach to include patients with unresectable primary carcinomas in the peritoneal cavity as well as those with diffuse abdominal carcinomatosis.

Wangensteen and his associates (1, 10) have long recognized the tendency for many intra-abdominal carcinomas to remain within the peritoneal cavity for relatively long periods of time before distant metastases occur. Indeed, patients frequently expire with diffuse involvement of the liver, peritoneum, and other abdominal viscera from carcinoma of the stomach, colon, pancreas, and ovaries and fail to show disease beyond the confines of the peritoneal cavity at autopsy. Our efforts have been directed toward development of a safe technique for providing as near total isolation of the peritoneal cavity and its contained organs as possible during a prolonged perfusion of the abdomen with blood containing anticancer agents. Paramount in this approach has been the necessity of preventing contamination of the remaining portions of the body with the highly potent cancericidal drugs.

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DEVELOPMENT OF SURGICAL TECHNIQUES

Initially our plan was to enter the left side of the chest through a thoracotomy incision, control aortic flow by cross-clamping just above the diaphragm, and perfuse through catheters placed in the right (or left) common femoral artery and vein. Return flow to the pump oxygenator through the inferior vena caval catheter was to be controlled so that only the amount of blood perfused through the artery was to be withdrawn, leaving a static condition of flow in the inferior vena cava at the diaphragm. However, initial studies in the laboratory and on the first 3 patients indicated failure of this technique adequately to control contamination of the thoracic portion of the body with the blood perfused into the abdominal aorta.

It soon became apparent that a "balance" between blood returning to the heart and that being drawn to the pump oxygenator was not sufficient, and more complete isolation of the peritoneal cavity from the thorax was needed. We then changed to a right thoracotomy incision and controlled the inferior vena cava with a Romel tourniquet while attempting to control the aorta from the right side of the patient. Technical difficulty was encountered in operating across the mediastinum in the human although this was readily accomplished in the dog. Therefore, in the human we settled upon a transverse bilateral thoracotomy approach which facilitated ligation of the internal

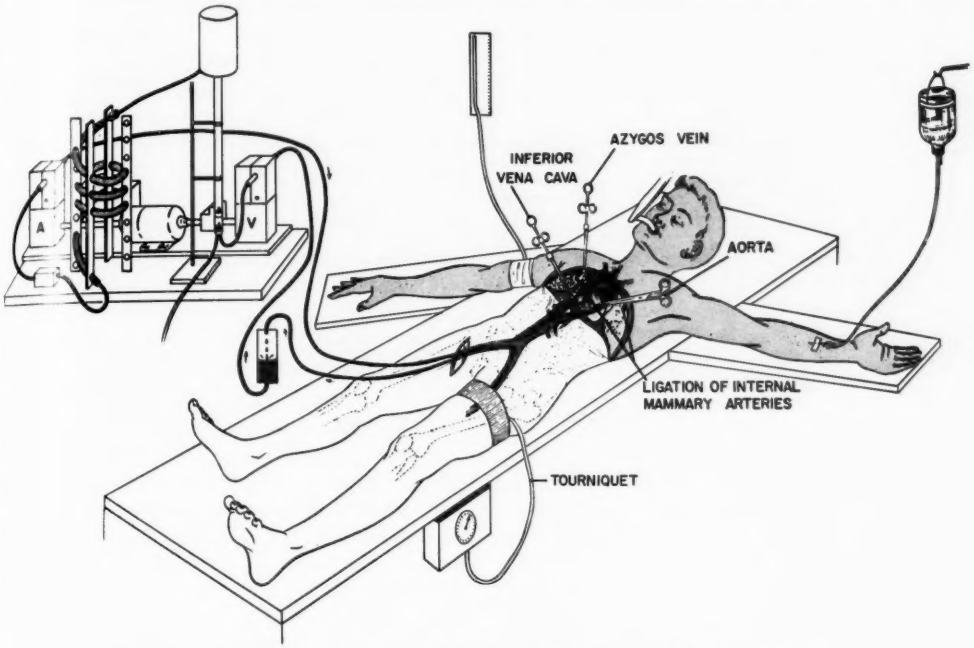

FIG. 1. Illustration of the operative approach that has proved most satisfactory.

mammary arteries and veins in addition to providing easy access to the aorta and inferior vena cava. Figure 1 demonstrates the operative approach that has proved most satisfactory.

ANIMAL STUDIES

Adult mongrel dogs have been used during development of the operative procedure to study the degree of mixing between the cardiopulmonary-thoracic circuit and the abdominal-pump-oxygenator circuit. Pressures in each circuit have been monitored with catheters placed in the carotid and femoral arteries. Evans blue dye has been used to determine the degree of intravascular mixing during the course of the 20 to 30 minute perfusions.

Figure 2 shows the basic arrangement for the animal studies with the abdominal circuit stippled. For 3 to 4 minutes after starting the perfusion the total circulation of the animal and the pump oxygenator were permitted to come to equilibrium prior to cross-clamping the major vessels; simultaneously the aorta, azygos vein, and inferior vena cava were clamped. Figure 3 shows the differential concentration pattern obtained in the dog studies after a high concentration of dye is injected into the abdominal circuit; a very slow rise of concentration of dye in the thoracic circuit occurs after a period of 15 to 20 minutes. In these experiments the dye was injected over a period of 10 minutes, and the continued mixing is evident from the slope of the curve in the thoracic circuit. The concentration of dye in the two circuits came to equilibrium quickly just as soon as the perfusion was stopped and the clamps were removed from the major vessels.

In the animal studies, flow rates of 300 to 700 cubic centimeters per minute have been used, and at 300 cubic centimeters per minute flow the blood pressure in the thoracic circuit has remained in the neighborhood of 80 to 100 millimeters of mercury; commonly the blood pressure in the ab-

TABLE I.—SUMMARY OF TOTAL ABDOMINAL PERFUSION CASES

Case No.	*Age, yrs.*	*Diagnosis*	*Operations*	*Perfusion data*	*Course and adjuvant drugs*
1	52	Metastatic adenocarcinoma of sigmoid colon	4-28-59 transverse colostomy; 5-19-59 exploratory laparotomy	6-23-59 HN_2-0.32 mgm./kgm. lt. thoracotomy; occlude aorta only; 6 mins. on pump	Temporary relief pain. Pathologic fracture lt. hip. Expired (8-11-59)
2	56	Metastatic adenocarcinoma of pancreas	4-2-59 exploratory laparotomy, cholecystojejunostomy, and jejunojejunostomy	7-10-59 30 mgm. Thiotepa (0.43 mgm./kgm.) lt. thoracotomy; aorta occluded 21 mins.	Benign postoperative course. Mild jaundice. Expired (12-23-59). Infarction right lobe of liver and spleen
3	57	Metastatic adenocarcinoma of cecum	6-12-59 resection ascending colon and primary anastomosis	7-31-59 45 mgm. Thiotepa (0.63 mgm./kgm.) lt. thoracotomy; aorta occluded 17 mins.	Expired Dec. 1959. Abdominal carcinomatosis
4	46	Metastatic cystadenocarcinoma of ovaries	4-20-53 panhysterectomy plus irradiation	8-7-59 75 mgm. Thiotepa (1.35 mgm./kgm.) rt. thoracotomy; IVC and aorta occluded 20 mins.	Benign course; moderate pancytopenia. No change in tumor. 11/4—11/11/59 200 mgm. cytoxan IV q. d.; condition satisfactory
5	46	Malignant hepatoma	7-5-59 exploratory laparotomy	8-13-59 287 mgm. 5-FUDR (5 mgm./kgm.) lt. thoracotomy; IVC and aorta occluded 31 mins.	Decreased tumor size; 3 monthly courses 5-FUDR IV. Expired (2-7-60)
6	43	Metastatic cystadenocarcinoma of ovary	1-18-59 exploratory laparotomy	8-14-59 570 mgm. 5-FUDR (10 mgm./kgm.) lt. thoracotomy; IVC and aorta closed 25 mins.	Severe thrombocytopenia, GI hemorrhage; tumor smaller. 10/28—11/2/59 5-FUDR, IV 5 d (25 mgm./kgm.). Doing well
7	66	Metastatic cystadenocarcinoma of ovary	9-8-59 exploratory laparotomy	9-22-59 90 mgm. Thiotepa (1.5 mgm./kgm.) sternal split; azygos, IVC, aorta occluded 24 mins.	Pancytopenia, staph. septicemia, hemorrhage. Expired (10-4-59)
8	72	Metastatic adenocarcinoma of colon	9-16-58 palliative resection splenic flexure	9-24-59 80 mgm. leukeran (1.9 mgm./kgm.) transverse sternal split; azygos, IVC, aorta occluded 25 mins.	Benign course, liver palpable 11-3-59. Feels well to present
9	42	Nonresectable carcinoma of pancreas	12-17-59 choledochoduodenostomy	1-22-60 120 mgm. HN_2 given in 3 separate injections of 40 mgm. each. One-fourth total body mass treated with high dosage (1.76 mgm./kgm. of total body) or (7.04 mgm./kgm. of treated tissue)	Benign course; mild hematuria for 18 hrs. Recovered. Well to present

dominal circuit has dropped to 25 to 40 millimeters of mercury but has immediately improved as the clamps on the major vessels have been released. The concentration of dye in the abdominal circuit has routinely approached 6.5 to 7 micrograms per cubic centimeter at the highest point in contrast to a concentration of dye in the thoracic circuit in the range of 1.5 to 2 micrograms per cubic centimeters at the end of 15 to 20 minutes of perfusion. Satisfactory and significant sequestration of the total abdominal cavity viscera can apparently be obtained by this method.

CLINICAL EXPERIENCE

Nine patients have been treated with this method of abdominal cavity perfusion by using 4 different anticancer agents. All have had either a nonresectable primary cancer found at previous laparotomy or proved carcinomatosis which followed a previous resection for cancer. Table I lists our clinical experience and demonstrates that 3 patients have had metastatic cystadenocarcinoma of the ovary, 3 have had metastatic carcinoma of the colon, 2 have had unresectable carcinoma of the pancreas, and 1 patient has had a large and extensive malignant hepatoma.

The first 3 patients had only the thoracic aorta cross-clamped according to our initial approach, and dye studies indicated that more intermixing of blood occurred than was desirable. In the operations performed in Cases 4, 5, and 6, both the inferior vena cava and aorta were closed, and there was improvement in the selective concentrations between the two circuits. In Cases 7, 8, and 9, the azygos vein as well as the aorta and inferior vena cava was ligated, and it was immediately apparent that isolation of the upper and lower circuits was more nearly complete. The following plan of operation is now recommended using a bilateral transverse thoracotomy at the level of the fourth interspace.

The aorta is freed up and a twill tape placed just above the diaphragm preparatory to cross-clamping with a vascular clamp. The pericardium is opened widely on the right side, and by blunt dissection a twill tape is placed around the inferior vena cava from the intrapericardial surface and a Romel tourniquet applied. A third twill tape is placed about the azygos vein in the right side of the chest to prepare the vein for closure with a Romel tourniquet at the proper time.

Concomitantly, a second operating team opens the groin (preferably the right side) and prepares the femoral artery and vein for cannulation. At this point of the operation the patient is heparinized with 1 milligram of heparin per kilogram of body weight, and the largest sized arterial and venous catheters which will comfortably fit the vessels are threaded up into the abdominal aorta and the inferior vena cava to the level of the celiac axis. The catheters are connected to the pump oxygenator and the patient readied for perfusion.

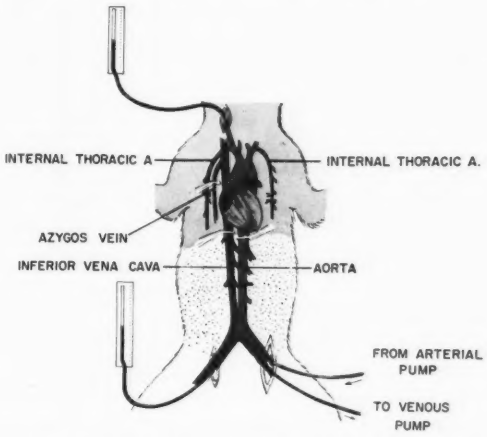

FIG. 2. Basic arrangement for the animal studies with the abdominal circuit stippled and the thoracic circuit in gray.

Upon starting the pump oxygenator the tourniquet on the thigh opposite to the cannulated vessels is pumped up to a pressure of 400 millimeters of mercury. The pump oxygenator is run for 2 to 3 minutes permitting a balance of the system, and at a given moment the azygos vein, the inferior vena cava, and the thoracic aorta are occluded in that order. It has been our experience that with this procedure of stabilization of the pump oxygenator flow and sequential cross-clamping of the major vessels the patient's blood pressure can be maintained in the thoracic circuit in the range of 120 to 140 millimeters of mercury throughout the entire 30 minute perfusion. On occasion it is necessary to elevate or lower the venous pool (Fig. 1) and thus slightly slow down or increase the rate of outflow from the inferior vena cava.

Rapid injection of the drug at the start of the selective perfusion after the major vessels

TABLE II.—DOSAGE OF VARIOUS DRUGS USED IN ABDOMINAL PERFUSIONS

Case No.	*Type of cancer*	*Drug*	*Dosage, mgm./kgm.*	*Usual total dose, IV or IM, mgm./kgm.*
1	Colon	HN_2	0.32	0.4—divided
2	Pancreas	Thiotepa	0.43	0.8—1.0 divided
3	Colon	Thiotepa	0.63	0.8—1.0 divided
4	Ovary	Thiotepa	1.35	0.8—1.0 divided
5	Malignant hepatoma	5 FUDR	5.0	15.0 × 5 days
6	Ovary	5 FUDR	10.0	15.0 × 5 days
7	Ovary	Thiotepa	1.5	0.8—1.0 divided
8	Colon	Chlorambucil (I.V.)	1.9	0.1—0.2 oral × 30 days
9	Pancreas	HN_2	1.76 (120 mgm.) (7.04 mgm./kgm. of mass of tissue treated)	Up to 1.5 mgm./kgm. for total body

are occluded gives an immediate high concentration in the abdominal circuit. When rapid acting drugs are used the injected drug is quickly inactivated in the tissues (approximately 5 minutes for nitrogen mustard), and a second injection can immediately follow. As many injections of drug can be given as desired according to a prearranged dosage schedule and the length of perfusion time. At the completion of the perfusion, after the last injected dose of anticancer agent has been inactivated in the tissues of the abdominal circuit, the pump oxygenator is stopped and simultaneously the azygos vein, the inferior vena cava, and the aorta are released. The artery and vein are sutured with No. 5-0 vascular silk and the pericardium is approximated with interrupted sutures of No. 3-0 silk; the chest is closed in the usual manner using suction drainage catheters in both pleural spaces. Flow rates ranging from 1,200 to 2,000 cubic centimeters per minute—20 to 30 cubic centimeters per kilo of weight—have been used in the clinical cases, and a flow rate in the neighborhood of 1,200 cubic centimeters per minute is now recommended for an average sized adult. Protamine is given after the cessation of the perfusion if undue bleeding is present.

COMPLICATIONS AND TOXICITY OF DRUGS

After reported work from other clinics several types of anticancer agents have been used in this developmental work. In Table II is presented the drug and dosage used for each type of cancer. Nitrogen mustard has been used for 1 patient with cancer of the colon and in 1 patient with a cancer of the pancreas. Thiotepa has been used in 1 patient with a cancer of the pancreas, 1 patient with a cancer of the colon, and 2 patients with cancer of the ovary; 5-fluorodeoxyuridine (5 FUDR) has been used in 1 patient with a malignant hepatoma and in 1 patient with a cancer of the ovary; chlorambucil (intravenous preparation) has been used in 1 patient with a cancer of the colon. We are satisfied that these agents, at the present time, do not represent the most effective and useful chemicals for this type of anticancer therapy.

With the exception of nitrogen mustard the length of time during which these drugs are active in the body is too prolonged for rational use with the intra-arterial perfusion technique. Complications resulting in 4 patients are portrayed in Figure 4, and it is immediately apparent that the most serious sequelae from the perfusions were due to the longer acting drugs. One patient being treated for a diffuse abdominal carcinomatosis secondary to a cystadenocarcinoma of the ovary had a severe thrombocytopenia following an intra-arterial dose of 570 milligrams of 5 FUDR. This patient hemorrhaged severely from the gastrointestinal tract, and it was necessary to use hypothermia at a level of 86 degrees F. for a period of 8 days to relieve the hemorrhagic diathesis; the patient subsequently recovered and is doing well. We believe that 5 FUDR is not well suited for this particular technique.

A second patient suffered a severe pancytopenia with a white blood cell drop to 0 on the eighth postoperative day as she was being treated for a diffuse involvement of the peritoneal cavity from cystadenocarcinoma of the ovary. In this instance 90 milligrams of THIOTEPA were given during the perfusion, and the prolonged action of the drug undoubtedly lead to the persistent leucopenia and death on the twelfth postoperative day from overwhelming infection. This woman represents the only early death following the perfusion procedure in these 9 patients.

A mild hepatic toxicity was noted in the patient with malignant hepatoma treated with 287 milligrams of 5 FUDR. We calculated this dose very carefully after performing critical experiments in dogs perfusing the portal vein with the drug and determining the highest concentration tolerated without apparent hepatic toxicity. The bromsulphalein reaction was high for a few days and then returned to normal shortly after recovery from the operation. The fourth patient to manifest a complication was the last patient in our series who was treated with 120 milligrams of nitrogen mustard for an unresectable carcinoma of the pancreas. This patient had a mild hematuria for a period of 18 hours after the perfusion, but there have been no late sequelae after recovery from the operation.

POSSIBILITIES WITH FRACTIONAL THERAPY IN ISOLATION PERFUSION TECHNIQUE

During perfusion of our last patient (Case 9) we utilized the technique of fractional injection of the anticancer agent (in this case nitrogen mustard) and believe a significant increase in dosage of drug to the cancer bearing areas can be effected in this way. This 42 year old man, weighing 73 kilograms, had previously had an end-to-side choledochoduodenostomy to relieve an extrahepatic biliary obstruction secondary to an extensive carcinoma of the pancreas. Six weeks after laparotomy he was perfused as outlined previously; in this instance we selected nitrogen mustard, and used it in 3 aliquots of 40 milligrams per injection. The total dose of 120 milligrams of drug represented 1.76 milligrams per kilogram total body dose, or, in effect, 120 milligrams to the abdomen which represents approximately one-fourth of the total mass of the body. This patient, then, received a total dosage of nitrogen mustard to the area treated which is approximately 4 times that used for maximal total body therapy with this agent. He experienced only an insignificant drop in the white blood cell count and a mild depression of platelet count postoperatively. We believe these clinical facts alone indicate the protection afforded to the patient's bone marrow by isolation perfusion,

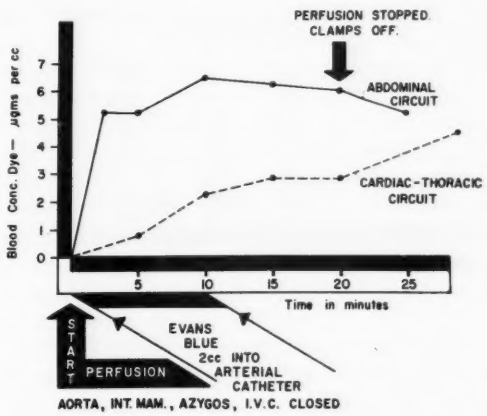

FIG. 3. Differential concentration pattern in the dog.

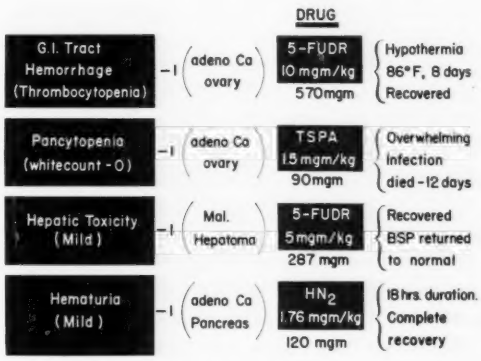

FIG. 4. Complications.

as well as the benefit to be derived from fractional injection of the drug.

In Figure 5 the differential concentrations of nitrogen mustard between the abdominal circuit and the thoracic circuit are graphically portrayed, and it is apparent that the drug, when injected rapidly (and of the short acting type) escapes from the abdominal-pump oxygenator circuit to the cardiopulmonary-thoracic circuit in only minimal amounts during each of the fractional injections. The effective concentration in the abdominal circuit is represented in Figure 5 by the heavy black areas, and the minimal concentration escaping into the thoracic circuit is represented by the stippled areas. The abdominal viscera and the cancer tissue in this instance were subjected to a dose of nitrogen mustard equal to 4 times the recognized maximum tolerated dose, and the functions of vital organs were not significantly altered. We believe that maximal efforts should be expended to produce short acting anticancer agents with increasing potential for carcinolytic action. It is obvious that the shorter the action time of any given drug the more useful that drug will become with perfusion techniques of this type. Perfusions could easily be prolonged to 60 to 80 minutes and afford an opportunity to repeatedly treat more cells coming into a receptive phase of their mitotic activity during this prolonged perfusion time.

DISCUSSION

Creech and his associates reported in 1957 the first experience with chemotherapy of cancer using an extracorporeal circuit to perfuse isolated areas of the body (8). These investigators have enlarged upon their initial experimental and clinical data and have worked out excellent techniques for selectively perfusing limbs, small and large bowel, lungs, pelvis, and breast (4–6, 9). They have postulated several specific advantages for this method of therapy; namely, (1) the minimal toxic systemic effects that are experienced, (2) the achievement of higher local concentrations of the anticancer agent, (3) administration of the agent under pressure to assure an adequate dissemination of the drug, (4) the fact that longer acting agents remain in contact with the tissue for duration of the action while shorter acting agents can be given in small repeated doses to maximum tolerance, (5) a high oxygen tension is maintained, and (6) the residual agent can be readily washed out of the isolated operative bed. In their extensive series these investigators have perfused patients who had several types of malignant tumors and have found sarcomas to respond better than adenocarcinomas.

Austen and his co-workers and Monaco and Austen using an isolated perfusion technique have reported a small series of patients with malignant pelvic tumors and 2 patients with Kaposi's sarcoma. These workers have found that perfusion can be performed in previously irradiated areas without serious sequelae and, in addition, point out that a rather large amount of drug can be given to a localized area without systemic reaction or undue complications. They have suggested the use of irradiation and perfusion in combination and also the possibilities inherent in using two drugs concomitantly during a given perfusion. In performing the perfusions these workers have stressed the benefit derived from holding extracorporeal perfusion pressure (3) approximately 30 millimeters of mercury below those of the systemic circuit in the remainder of the body.

During recent months Aust and Ausman at the University of Minnesota have reported the maximal tissue absorption of nitrogen mustard during perfusion in dogs to be present with lower than maximum oxygen tensions in the perfused blood. These studies are of great interest and indicate that, at least in respect to the uptake of nitrogen mustard in normal tissues, excessive oxygenation of perfused blood is not necessary and possibly is to be avoided. However, the relationship of oxygenation of perfused blood and nitrogen mustard uptake by cancerous tissue needs to be clarified. When this technique of perfusion is used for the total ab-

dominal viscera as described herein adequate oxygenation of vital organs such as the kidney and liver probably is important to success; standard oxygen tensions in perfused blood seem to be indicated here.

In our approach we have considered the possibility of using femoral arterial and venous catheters equipped with occlusive balloons to tamponade the aorta and inferior vena cava. However, our experience indicates that total occlusion of flow through these major vessels is paramount to success of the procedure. An adequate tamponade effect could not be achieved, at least in the aorta, by the intravascular balloon technique.

In reviewing the relationship of this operative procedure to the problem of chemotherapy for the types of cancer involved, we believe there is a distinct advantage in not entering the abdominal cavity containing cancer at the same time that vigorous chemical therapy is given. Further, by this procedure occult and diffuse metastases in the total peritoneal cavity and the organs contained therein are all treated at one time with a significant high flow of treated blood to all areas. The results from the animal studies and the later clinical cases would indicate that this approach protects the larger areas of bone marrow significantly from exposure to the toxic effects of the drugs used.

Of greatest interest are the possibilities inherent in this technique when short-acting anticancer agents are used. An intensive effort should be expended on the part of the biochemists interested in the problem of anticancer therapy to develop further alkylating agents of an increasingly short action time which can be adapted to perfusion techniques for the various areas of the body. The dismal results from all clinics in the group of patients with unresectable or advanced cancers of the peritoneal viscera indicate to us that any effort we make toward salvage of even a small portion of this group is of value. With application of the "second look" plan Wangensteen has been able to salvage some patients with widespread abdominal metastases after repeated operations; often as many as 5 laparotomies have been performed after the major resection of the primary tumor. But, even in this courageous and brilliant approach, it is apparent that the tumor frequently stays just ahead of the surgeon's scalpel as the months go by. Perhaps, with a concentrated effort between cancer biologists, biologic chemists, and surgeons aiming to produce more effective and shorter acting anticancer agents some additional inroads can be made into this grim problem of the patient with unresectable or widespread carcinoma of the peritoneal cavity.

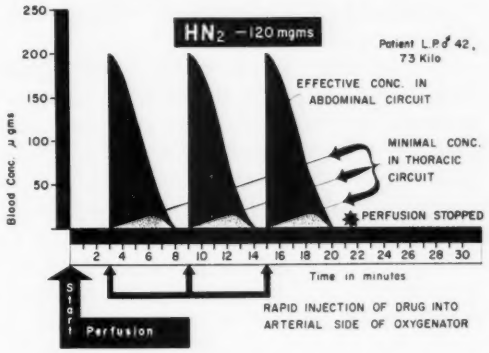

FIG. 5. Differential concentrations of rapidly inactivated anticancer drugs with abdominal isolation perfusion technique.

SUMMARY

1. A method for isolation of the abdominal cavity and its viscera during intra-arterial perfusion has been presented. The differential concentrations obtainable between the abdominal-pump oxygenator circuit (6 to 7 micrograms) and the cardiopulmonary-thoracic circuit (1.5 to 2 micrograms) appear satisfactory.

2. Clinical experience with 9 patients has been reported; no operative deaths have occurred, but 1 patient died of serious leucopenia on the eighth postoperative day.

3. Evidence indicating the value of repeated injections of rapid-acting anticancer agents has been presented and the minimal contamination of the cardiopulmonary-

thoracic circuit under these circumstances has been emphasized.

4. The clinical experience in this study demonstrates that large doses of nitrogen mustard (4 times the reported maximum dose for nitrogen mustard reported in the literature) can be given when the major bone marrow areas of the body are protected as outlined in these studies.

5. The need has been emphasized for an accelerated program aiming to produce more effective anticancer agents particularly of the short action, or labile, type.

6. With the appearance of more effective carcinolytic drugs, selective total abdominal cavity perfusion offers a reasonable chance for future significant benefit to patients suffering from unresectable abdominal carcinomas or carcinomatosis of the peritoneal cavity.

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A STUDY OF COMPLICATIONS IN THE SURGICAL AND RADIATION THERAPY OF CANCER OF THE CERVIX

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EFFORTS to improve the cure rate in cancer of the cervix by increasing the extent of surgical treatment or the dosage of radiation have resulted in an inevitable rise in the frequency of injuries. Although a certain number of injuries are acceptable in the treatment of a disease that is so often fatal, nevertheless a point must be reached where complications bar further extension of therapy.

This study was undertaken; (1) to compare radiation and surgical methods of treatment with respect to their complications which offer criteria for selection of therapy only less important than the respective cure rates; (2) to try to define the limits of therapy, particularly the dose levels of radiation, at which the complication rate seems to become so great as to preclude further increases in therapy.

At the Presbyterian and Francis Delafield Hospitals during the years 1944 to 1957, 748 patients with primary carcinoma of the cervix were observed. These patients were treated by the following methods: (1) external roentgen rays alone, 82 patients; (2) intracavitary radium and external roentgen rays, 272 patients; (3) radium needles and external roentgen rays, 119 patients; (4) intracavitary radium, external roentgen rays and lymph node dissection, 56 patients; (5) radical operation, 92 patients; (6) radical operation and external roentgen rays, 115 patients; and (7) other, 12 patients.

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The 5 year end results of the 359 patients treated from 1944 to 1951 have already been reported (12). Certain changes were made in the management of cervical cancer at these hospitals in late 1951 and early 1952. For these reasons, the series will be reported in 2 periods, 1944 to 1951 and 1952 to 1957.

The most characteristic changes in the later period were two: From 1952 to 1957 some patients underwent extraperitoneal node dissection after full radium and external roentgenotherapy. Furthermore, supervoltage therapy was introduced, and the tumor dosage of external radiation was gradually increased from the 2,500 to 3,000 roentgens given over a period of 4 weeks in the 1944 to 1951 series to about 6,000 roentgens given in 4 to 6 weeks in 1955 to 1957. The radium dosage, however, was kept at approximately the same level during the entire period from 1944 to 1957.

The injuries produced by these methods of therapy will be considered in 3 categories, namely, radiation injuries, surgical injuries, and those due to a combination of both.

NATURE AND REPORTED FREQUENCY OF RADIATION INJURIES

There is a considerable literature on injuries resulting from the radiation treatment of carcinoma of the cervix, but reports on supervoltage injuries are scarce. The various types of radiation injuries may be classed as intestinal, urinary, osseous, and cutaneous.

Gastrointestinal tract. Warren and Whipple demonstrated experimentally the susceptibility of the intestinal mucosa of dogs to

roentgen irradiation in 1921. In human beings, damage manifests itself by symptoms appearing during treatment, or signs of it may be delayed as long as 15 years after therapy.

According to Warren and Whipple, the epithelial cell of the intestine is one of the most radiosensitive cells in the body. The stenosis which is characteristic of most late bowel injuries, however, is probably secondary to an endarteritis or thrombosis of the blood vessels supplying the area of intestine involved.

Clinically considered, the process starts with an enterocolitis characterized by nausea, diarrhea, blood in the stool, and perhaps degrees of prostration. These symptoms occur while therapy is still in progress or immediately afterward and probably are due to the specific effect of irradiation upon the intestinal mucosa. Often these patients lose weight and appear poorly nourished. The late symptoms, bowel obstruction, perforation, or peritonitis, probably are the result of endarteritis and fibrosis. Recent work has shown that the absorption from the bowel as well as its motility are adversely affected by roentgenotherapy.

Urinary tract. A mild cystitis and, in some, moderate hematuria develop in most patients treated by intracavitary radium and external radiation. In a few, severe hemorrhagic cystitis later develops, necessitating repeated blood transfusions for a year or more after therapy. Occasionally, the pathologic process progresses to vesicovaginal fistula or, in the most severe instances, complete bladder necrosis. There are occasional ureteral obstructions secondary to persistent fibrosis after external irradiation. The latter injury was not seen in our series until the recent trend toward increased external dosage.

According to Corscaden, the urinary epithelium is less susceptible to roentgen and gamma rays than is the epithelium of the rectosigmoid. Radiation delivered to the base of the bladder causes much less damage than is caused in the rectum by the same number of roentgens. Gray and Kottmeier (14) report, in 204 cases of stages I and II a, 1.0 per cent serious bladder injuries as compared with 3.9 per cent rectal injuries; in 261 cases of stages II b, III, and IV there were 2.7 per cent serious bladder injuries and 9.6 per cent serious rectal injuries. Brack, reporting on a series of patients treated by a combination of roentgenotherapy and radium, noted urinary tract injuries in 49 of 402 patients or 12.2 per cent. In the series were 5.4 per cent with vesicovaginal fistulas, 2 per cent with both rectovaginal and vesicovaginal fistulas, 1.2 per cent with late radiation ulcers of the bladder, and 0.5 per cent with rectovaginal fistulas. A death was also reported by the same author from radiation fibrosis of the ureters.

Pelvic bones. After irradiation for cancer of the cervix, a small percentage, less than 2 per cent, of hip fractures occur. These usually happen later than the complications from the bowel or urinary tract, being delayed from 1 to 2 years or more after treatment. Smith believes that this is a fatigue type of fracture resulting from continued weightbearing on a hip weakened in its blood supply and bony strength by the heavy irradiation.

Baensch in 1927 was the first to report on hip fracture after pelvic irradiation. Dalby and associates reported a series of 14 cases in this country in 1936, an incidence of 2.1 per cent of the cases treated. Smith reported 8 instances of fracture of the femoral neck after pelvic irradiation in 1954 at the Presbyterian Hospital in New York. Dosages that produced the fractures in these series varied greatly, so that a fracture producing dose cannot be arrived at by examining the data.

Skin injuries. Skin injuries formerly played an important part in the radiation complications but, since supervoltage became available, skin injuries are rare.

Effects of supervoltage and increased tumor dosage. Until the advent of supervoltage, the dosage of external radiation to the pelvis

was limited by skin tolerance. For this reason it was difficult to give more than a 3,000 roentgen tumor dose in 1 month to the pelvis by external radiation, and radium was relied upon to treat the primary tumor. Practically all injuries hitherto reported as following irradiation were caused by intravaginal and intracavitary radium. From experience with radium, data are available to show the dose levels at which some injuries may be expected.

Ingelman-Sundberg reviewed 109 cases and concluded that rectal complications were more common when more than 3,300 roentgens were delivered to a point 8 centimeters away from the anterior rectal wall. Deeley, after experience with the Curie technique, concluded that proctitis occurs in 23 per cent of patients in whom the rectal dose is between 4,000 and 4,500 roentgens and in 35 per cent of the patients in whom the dose is 5,400 roentgens. In his experience, severe damage occurred in only 16 per cent of patients receiving less than 4,000 roentgens. Gray and Kottmeier (14) found that a significant increase in rectal injuries occurred when the radium dosage to the rectum exceeded 2,400 roentgens in 24 hours.

With supervoltage therapy, it is possible to deliver increasingly larger tumor doses. Not enough time has elapsed to find out whether or not increasing the dosage has cured more patients, but there are a few reports which suggest that the incidence of injuries has increased.

Wall reported 5 major complications in 24 patients treated by radium and roentgen rays who received more than a 4,000 roentgen tumor dose by external irradiation. There were 2 major complications in 25 patients treated by radium and a 3,500 to 4,000 roentgen tumor dose by external irradiation and only 1 in 49 who received 3,000 to 3,500 roentgens by roentgenotherapy. He concluded that tumor dosage from external irradiation should not exceed 3,500 roentgens.

Cowell reported severe reactions in 59.5 per cent of her radium treated patients given 4,500 to 5,500 roentgens to point "A", supplemented by 4,000 roentgens from external irradiation, delivered in 4 weeks, using a 4 field technique. She concluded that the use of large field supplementary roentgenotherapy by obliquely directed portals, resulting in a large volume of the pelvis being irradiated with the superimposition of radium and roentgen ray dosage at the center, is hazardous and should be abandoned.

Fletcher and associates, on the other hand, state that there is no evidence of absolute levels for the radiation tolerance of the bladder and rectum and believe that one should not set up radium techniques based on such figures. They also state that there is a wide range of dose levels within which gradual increase in the incidence of complications probably will occur. Precisely defined levels are valid for only one radium and external radiation technique and one method for obtaining physical data.

Deaths from radiation therapy. Not many articles have reported deaths due to complications resulting from treatment by radium and roentgen rays. Gray and Kottmeier reported 1 immediate death due to peritonitis among 500 cases. Truelsen reported 47 deaths among 2,437 patients treated, or 1.93 per cent. Brack reported 10 cases of massive radiation necrosis in 402 patients with 3 deaths attributed to radiation injuries. The ultimate fate of 204 patients who had survived 5 years after radiotherapy for cancer of the cervix at the Toronto Clinic was reviewed by Cosbie. In the author's opinion "postradiation fibrosis presented not only a diagnostic problem but alone or in association with recurrent or temporarily controlled cancer caused ill health which ultimately ended in the deaths of at least 21 patients."

REPORTED FREQUENCY OF SURGICAL COMPLICATIONS

With the reintroduction of radical surgery, there have been complications asso-

TABLE I.—FREQUENCY OF COMPLICATIONS IN WERTHEIM'S FIRST 500 CASES ANALYZED IN 1911 IN COMPARISON WITH MEIGS' FIRST 473 CASES ANALYZED IN 1955

	Wertheim, 1911, 500 cases, per cent	*Meigs, 1955, 473 cases, per cent*
Operative mortality	18.6	1.7
Fistulas or strictures	9.3	10.9
Infections, pelvis and abdominal wall	17.0	4.9
Other complications	5.2	8.2

ciated with this form of therapy. These complications can be divided into operative, immediate postoperative (within the first 14 days after operation), and late complications.

Operative complications. Hemorrhage from the pelvic veins during operation is one of the most common technical difficulties and can result in death of the patient on the operating room table or force the surgeon to terminate the procedure with an inadequate operation. With modern anesthesia and supportive measures, such severe operative complications are rare.

Immediate postoperative complications. Localized or diffuse peritonitis was formerly one of the commonest postoperative complications, but now, because of antibiotics, the condition is not very common. Paralytic ileus is also not frequently seen if patients are not fed orally until bowel sounds are heard and gas is passed per rectum. With such a regimen parenteral administration of fluids and control of electrolyte balance are imperative.

Late postoperative complications. The most important late surgical complication is the ureterovaginal fistula whose incidence remains fairly constant. Meigs reports it to be 10 per cent; Douglas and Birnbaum, 9 per cent; Thomas and associates, 12 per cent; Kelso, 8.6 per cent; St. Martin and associates, 30 per cent; Peterson and Hornbrook, 14 per cent; Bonney, 3 per cent; and Read, 3.1 per cent. Besides ureterovaginal fistulas, there is the occasional case of atony of the bladder, persisting for more than a year. Intestinal fistulas as a surgical complication are not very common as contrasted to those that follow radiotherapy in which injury to the rectum is one of the most common complications. Intestinal obstruction from postoperative adhesions requiring re-exploration is occasionally seen.

Declining complications and mortality rates in surgery. The operative mortality for the radical operation has greatly lessened as can be seen from the following figures: Wertheim, 19 per cent in 1911; Bonney, 14 per cent in 1941; Read, 8.3 per cent in 1948; Kelso, 2.1 per cent in 1952; and Meigs, 1.7 per cent in 1955. A comparison of the complications reported by Meigs and Wertheim was reported by Christensen and Lange and is given in Table I.

ANALYSIS OF COMPLICATIONS ARISING IN TREATMENT OF 748 PATIENTS WITH CANCER OF THE CERVIX

Changes in techniques as well as some differences in the type of case referred for either irradiation or operation make difficult a simple analysis of the complications resulting from the treatment of 748 patients of the present series. Some introductory comments are necessary to explain the various groups that have been set up.

Changes in technique during period of study. From 1944 to 1951, the majority of patients were treated by intracavitary radium in doses of 6,000 to 7,000 milligram hours followed by conventional deep roentgenotherapy, with an average dose to the tumor area of 3,000 roentgens in 4 to 5 weeks. The complications arising in this group will be separately considered and taken as reasonably representative of what may be expected with these moderate doses of external radiation. During these years, a number of patients, especially those in stages II and III, were treated with parametrial radium needles, the injuries from which obviously must be separately considered. Finally, a few patients in this period were treated by radical operation. The complications in these years were perhaps representative of what is to be expected when this technique is first practiced in a particular department.

TABLE II.—SUMMARY OF TECHNIQUES OF THERAPY IN 419 PATIENTS TREATED FROM 1952 TO 1957

	Radium, roentgenotherapy, and node dissection	*Radium and roentgenotherapy*	*External roentgenotherapy only*	*Surgery with and without roentgenotherapy*	*Palliation by roentgenotherapy*	*No treatment*	*Total No. of cases*
Stage I	25	56	0	60	0	0	141
Stage II	20	56	0	59	0	0	135
Stage III	3	18	39	9	0	2	71
Stage IV	0	2	13	2	17	3	37
Cervical stump cases	8	14	0	12	0	1	35
Total	56	146	52	142	17	6	419

Late in 1951, the Francis Delafield Hospital was opened for the care of indigent cancer patients. It has supplied an increasing volume of cases often, however, in a rather advanced stage.

With the opening of the Delafield Hospital, a 2,000 kilovolt roentgen ray therapy machine was at once available, and shortly thereafter rotational equipment for treatment with cobalt 60 was added. In 1955, the betatron with its 22.5 million volt roentgen ray beam became operational at the Presbyterian Hospital. With these high energy units, it is possible to administer much higher doses of radiation to the pelvis without skin damage. The average dose of external therapy for many types of gynecologic cancer was increased from a previous average of 3,000 roentgens in 4 to 6 weeks to 5,000 or even 6,000 roentgens in the same period of time.

A new formulation of indications for special types of therapy was also adopted in 1952, partly in an effort to provide parallel series of patients, the one treated primarily surgically, the other by radiation. The many exceptions made necessary by medical or constitutional contraindications to radical operation have diminished the value of these two series as strict controls of each other. There is, nevertheless, available for the study, a considerable list of patients treated by radiation, by operation, and by a combination of these methods.

During the 1952 to 1957 phase, the patients with the stage I and stage II lesions selected for surgical treatment underwent radical hysterectomy and lymph node dissection and, if any extension beyond the cervix was found, received postoperative roentgenotherapy with a tumor dose ranging from 3,000 to 6,000 roentgens over a 4 to 6 week period. The stage I and II patients of the radium and roentgenotherapy series were for the most part later subjected to surgical dissection of the lymph nodes. Patients with stages III and IV lesions, after a few surgical attempts were made, were managed at first by external radiation alone but later with the addition of a radium treatment. The summary of the techniques of therapy used in the 419 cases of primary carcinoma of the cervix in 1952 to 1957 is given in Table II.

Injuries and complications in the tables to follow will be reported as fatal, major, and moderate. A major complication is defined as one which necessitated another surgical procedure or resulted in a permanent disability. A moderate complication is one that was transitory, did not require extensive surgical intervention, and resulted in no significant incapacity.

Complications in patients treated with radium and roentgenotherapy, 1944 to 1951. From 1944 to 1951 the majority of patients were treated by radium and roentgen rays. The

TABLE III.—COMPLICATIONS FOLLOWING INTRACAVITARY RADIUM SUPPLEMENTED BY AN AVERAGE TUMOR DOSE OF 3,000 ROENTGENS EXTERNAL RADIATION IN 143 STAGE I AND II CASES, 1944 TO 1951

	Early	*Late*
Fatal	0	0
Major	0	2 Rectovaginal fistulas 1 Stricture of rectum 1 Vesicovaginal fistula 1 Necrosis of hip 2 Fractured femur
Moderate	0	3 Pyometra 4 Proctitis 3 Telangiectasis of sigmoid

FIG. 1. Case 1. Margin of ulcer in bowel with necrosis of muscularis mucosa and fibrosis of submucosa and muscularis. ×57.

5 year results have already been published (12). These patients were treated mainly by intracavitary radium and roentgenotherapy or by radium needles and roentgenotherapy.

Intracavitary radium and roentgenotherapy.—The standard technique for stages I and II consisted of 60 to 70 milligrams of radium inserted in 10 milligram sources with the usual Curie distribution for a period of about 100 hours. After radium treatment the patients were given tumor dose of about 2,500 to 3,000 roentgens to the midpelvis of 200 or 250 kilovolt radiation over a period of 4 to 6 weeks. With this technique there were only 7 major injuries, about 4.0 per cent, and no fatal results. The complications which occurred in this group are shown in Table III.

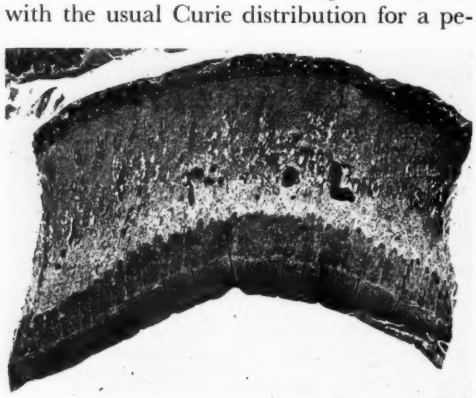

FIG. 2. Case 3. Great edema and fibrosis of submucosa and bleeding of small arteries. ×7.

Interstitial radium.—The radium needles technique and 5 year end results in 102 cases have already been published (12). For completeness, a summary of the injuries produced has been included in Table IV. There were 3 major complications and 2 deaths, one from intestinal obstruction and uremia and the other from pulmonary embolus secondary to cystotomy for hemorrhagic cystitis 1 year after the original therapy.

Complications in patients treated by radium, roentgen rays, and iliac lymph node dissection, 1952 to 1957. An extraperitoneal lymph node dissection was performed on the majority of the ward patients in stages I and II and in some stage III patients treated by radium about 6 weeks after the completion of roentgenotherapy, in the hope of removing metastatic disease which might not have been controlled by irradiation. The results of this combined procedure have been reported in two previous publications by Gray and her associates (13, 15). Table V shows the complications resulting from this form of therapy. The operation has been abandoned on this service because (1) it produces too many injuries; (2) all patients with persistent carcinoma in pelvic lymph nodes after irradiation have subsequently died of cancer despite the operation; and (3) some patients with negative pelvic lymph nodes died of disease persistent elsewhere in the pelvis. The many complications that follow this plan of therapy must be considered to be the result of a combination of irradiation and surgery.

Two case reports illustrate the severe tissue damage which may result from such combined therapy.

CASE 1. A 52 year old Puerto Rican woman with a stage I lesion was treated with a 3,000 roentgen tumor dose by means of the transvaginal cone with 250 kilovolts radiation from 8 August to 15 August 1955 followed by 2 radium applications on 19 August and 29 September 1955, in each of which an intrauterine tandem containing 30 milligrams and 3 vaginal plugs each containing 10 milligrams, as in the Curie technique, were left in place for 50 hours. After this therapy was completed, she received a tumor dose of 4,800 roentgens by cobalt 60 radiation through 2 opposing fields 15 by 15 centimeters in 5 weeks. Four months later, a transperitoneal pelvic node dissection was performed. The lymph nodes removed proved on pathologic examination to be negative for neoplastic disease.

During the next 2 years the patient had several episodes of small bowel obstruction. Two and one-half years after radiation therapy an ileovaginal fistula developed, several feet of ileum were resected, and an ileotransverse colostomy was performed. Pathologic examination showed the changes seen in severe radiation damage (Fig. 1).

The postoperative course was stormy and the patient eventually died of inanition 3 years after the original treatment. Autopsy showed no evidence of recurrent disease, but there was marked radiation change in the large and small bowel and bladder. Sections taken of the connective tissue even around the sacral nerves showed extensive fibrosis, apparently secondary to irradiation.

CASE 2. A 38 year old Negro woman with a stage I carcinoma of the cervix was treated with 50 milligrams of radium for 125 hours applied by modified Curie technique, 2 by 10 milligram sources, intrauterine tandem, and 3 by 10 milligrams in the vagina followed by treatment with 250 kilovolts roentgen rays given through 6 fields of 10 by 18 centimeters each for a total tumor dose of 4,100 roentgens in 1 month. An extraperitoneal lymph node dissection was performed 4 months after the completion of therapy. Seven months after her therapy an abscess developed in the left groin which was incised and drained. A vesicocutaneous fistula developed, followed later by a sigmoid cutaneous fistula. A transverse loop colostomy was performed. The patient is now living without evidence of disease 5 years after treatment but has a transverse colostomy and continually must wear an indwelling catheter.

Complications in patients treated by radium and roentgenotherapy, 1952 to 1957. There were 125 patients with stages I and II lesions treated by intracavitary radium followed by external roentgenotherapy. This group includes some patients who were considered unfit for either the radical hysterectomy and pelvic lymph node dissection or pelvic lymph node dissection after complete radium and roentgenotherapy because of their poor general physical condition. Here again, the technique has varied. In 1954, a preliminary test dose of 3,000 roentgens by vaginal cone was added to the

TABLE IV.—COMPLICATIONS FOLLOWING INTERSTITIAL RADIUM IN 102 STAGE II AND III CASES, 1944 TO 1951

	Early	*Late*
Fatal.....	0	1 Ulcer of the vaginal vault 5 months after therapy, retreated with radium producing ureteral obstruction, uremia, and death 1 Pulmonary embolus secondary to cystotomy for hemorrhagic cystitis 1 year after therapy
Major.....	0	1 Pyelonephritis secondary to severe radiation cystitis, nephrectomy necessary 1 Rectovaginal fistula 1 Osteomyelitis of the upper end of the femur
Moderate..	0	3 Hemorrhagic cystitis 3 Ulcer of bladder 2 Simple cystitis 4 Proctitis 3 Vaginal ulcers

TABLE V.—COMPLICATIONS IN 53 PATIENTS WITH STAGE I AND II LESIONS TREATED BY RADIUM, ROENTGEN RAYS, AND NODE DISSECTION, 1952 TO 1957

	Early	*Late*
Fatal.....	1 Intestinal obstruction following node dissection 1 Pulmonary embolus	1 Radiation fibrosis and necrosis of bowel 2 years post-therapy
Major.....	4 Retroperitoneal lymph accumulations requiring the following procedures: Incision and drainage, 3 Bilateral nephrostomy, 1 Uncorrected defects: Bilateral inguinal hernia, 1 Hydronephrosis, 1 1 Severe wound infection	1 Rectal stricture requiring colostomy 1 Rectovaginal fistula 1 Rectal stricture 1 Proctitis, severe 1 Aseptic necrosis of the right femoral head 3 Fracture of the femoral neck with bilateral ureteral obstruction in one 1 Combined vesicocutaneous and fecal fistula requiring colostomy 1 Pyelitis, severe with ureteral strictures 2 Severe leg edema
Moderate..	2 Incisional hematomas 1 Wound infection	3 Leg edema 3 Leg edema and cystitis 4 Cystitis 1 Cystitis and proctitis 2 Transitory proctitis 2 Transitory cystitis
Totals.....	10	28

TABLE VI.—COMPLICATIONS IN 125 PATIENTS WITH STAGE I AND II LESIONS TREATED BY RADIUM AND AN AVERAGE DOSE OF 5,000 TO 6,000 ROENTGENS EXTERNAL RADIATION, 1952 TO 1957

	Early	*Late*
Fatal.....	0	2 Radiation necrosis of the large and small bowel 1 Radiation necrosis of the large bowel 1 Hemorrhagic cystitis and stricture of the left ureter
Major.....	0	1 Rectal stricture and cystitis requiring colostomy 1 Rectovaginal fistula and obstructed ureters requiring colostomy and bilateral cutaneous ureterostomies 1 Necrosis of the ileum requiring small bowel resection, and hemorrhagic cystitis 1 Stricture of the ureter 1 Combined vesicovaginal and ureterovaginal fistula 1 Unilateral hydronephrosis requiring ureterostomy 1 Necrosis of the femoral head, bilateral
Moderate..	1 Severe diarrhea	8 Proctitis 1 Rectal stricture and cystitis 3 Pelvic thrombophlebitis, 1 with pulmonary embolus, nonfatal 2 Cystitis 1 Vaginal stricture requiring operation
Totals.....	1	26

radium technique and the radium application was divided into 2 parts. Some patients were treated by 250 kilovolt machine and others by the 2 million volt or betatron radiation. All these patients received intracavitary radium by the technique already described. The dosage was not increased over the levels given in 1944 to 1951.

The major complication rate was 7 of 125 cases or 5.5 per cent and the mortality rate was 4 of 125 cases or 3.2 per cent (Table VI). This mortality is higher than reported for most irradiation series. In addition 2 patients not included in the table succumbed while receiving radiotherapy. The first was a patient who died from sepsis after having received part of her external radiation therapy. The second death was due to a cerebrovascular accident which occurred while the patient was receiving external radiation. The 4 fatalities in Table VI were on the basis of rather extensive radiation damage to the bowel and occurred in patients who at the time of death were without proved disease. One case will serve as an illustration

CASE 3. A 51 year old gravida 0, para 0 was admitted in October 1956 with a stage IIb epidermoid carcinoma of the cervix. The patient had possible increased susceptibility to radiation injury, in that there was a history of allergies to many foods, and she had lost about 20 pounds in the 2 years preceding her admission. There were, however, no bowel symptoms prior to irradiation.

The patient received a 2,800 roentgen tumor dose to the pelvis with the 2 million volt machine through 2 opposing 15 by 15 centimeter fields over a period of about 3 weeks. The treatments were poorly tolerated and the patient was incapacitated by frequent attacks of diarrhea. Two weeks after the first part of her external irradiation, 60 milligrams of intracavitary radium were inserted by Corscaden applicator and left in place for 100 hours. Twelve days after this treatment a 2,600 roentgen tumor dose was given to the pelvis by 2 million volt roentgenotherapy during a period of about 3 weeks, using the same field size. Again the treatments were poorly tolerated and the patient had severe diarrhea.

During the next 4 months the patient continued to have diarrhea and lower abdominal cramps plus weight loss. She was admitted as an emergency case, and exploratory laparotomy was performed. A resection of terminal ileum and cecum plus ileocolostomy was performed because of ulceration and gangrene of the bowel secondary to irradiation (Fig. 2).

The patient recovered from the operation but continued to have loose bowel movements and back pain. Proctoscopy 5 months after the bowel resection and 9 months after the completion of radiation therapy showed proctitis and slough of the mucosa. A sigmoid colostomy was performed, but after operation slough of the vagina, rectum, and posterior wall of the bladder occurred. The patient died after an episode of bleeding from the colostomy 1 year and 1 month after the completion of radiotherapy. Autopsy showed rectovaginal and vesicovaginal fistulas secondary to irradiation. Necrosing radiation ileitis and colitis were also found in the lower ileum and rectosigmoid. There was no residual disease.

TABLE VII.—METHODS OF THERAPY AND COMPLICATIONS IN 73 PATIENTS WITH STAGE III LESIONS, 1952 TO 1957

Treatment	*No. of cases*	*Deaths*	*Complications*			
			Total	*Nonfatal*		
				Major	*Moderate*	*Minor*
External radiation only	39		3		3	
Rotation therapy	32	—	3	—	3	—
Cobalt, opposing fields	4	—	—	—	—	—
2 M.E.V.	3	—	—	—	—	—
External radiation and radium	20		2	1		1
Intracavitary radium and 250 kv.	2	—	1	1	—	—
Intracavitary radium and 2 M.E.V.	1	—	—	—	—	—
Interstitial radium and 250 kv.	8	—	1	—	—	1
Interstitial radium and betatron	4	—	—	—	—	—
Interstitial radium and cobalt	1	—	—	—	—	—
Interstitial radium and 2 M.E.V.	4	—	—	—	—	—
Operation and external radiation	7		3	1	2	
Radical hysterectomy, node dissection, roentgenotherapy	4	—	2	—	2	—
Anterior exenteration and roentgenotherapy	1	—	—	—	—	—
Exenteration and cobalt	1	—	—	—	—	—
Partial cystectomy, radical hysterectomy, and 2 M.E.V.	1	—	1	1	—	—
Operation, radium, and roentgenotherapy	4		3		3	
Rotation, intracavitary radium, and node dissection	1	—	1	—	1	—
2 M.E.V., intracavitary radium, and node dissection	1	—	1	—	1	—
Exploratory laparotomy, intracavitary radium, and node dissection	1	—	—	—	—	—
Exploratory laparotomy (inoperable), 2 M.E.V., intracavitary radium, and node dissection	1	—	1	—	1	—
Operation alone	1		1		1	
Total exenteration	1	—	1	—	1	—
Not treated	2	1	—	—	—	—
Totals	73	1	12	2	9	1

Radiation for stage III and stage IV cases, 1952 to 1957. There were 73 patients with stage III lesions treated from 1952 to 1957, therapy being given in a variety of ways (Table VII). About half of the series received a 5,000 to 6,000 roentgen tumor dose to the pelvis by cobalt 60 rotation in 6 weeks time. Radium was not used in most of the cobalt treated patients. The tumor dose to the primary lesion was therefore markedly reduced, 5,000 to 6,000 roentgens by cobalt alone, a figure to be contrasted to the more than 10,000 roentgens when the cervix is treated by radium and external roentgen rays.

Sufficient time has not passed to permit reporting 5 year survivals, but of the 36 patients treated in this fashion, 12 are now living between 1 and 5 years later. The injuries in the cobalt treated patients are low in spite of the high dosages of external radiation.

There were 34 patients in stage IV treated at the Presbyterian and Delafield Hospitals between 1952 and 1957 inclusive (Table VIII). Over half received no therapy or only palliative therapy because their lesions were too far advanced for hope of cure. The complications were not the result of therapy but of the advancing disease and accordingly need not be discussed in this report.

Complications in patients treated by operation, 1944 to 1951. From 1944 to 1951 there were 77 patients with primary lesions treated surgically. There was a large number of early cases in the group: 52 cases in stage I, 19 in stage II, 3 with stage I stump, and 3 with stage II stump.

All of these patients were not submitted to radical surgery. Nine had inadequate operations, because of either failure in diagnosis of the disease prior to operation or technical difficulties at the time of surgery. The following types of operation were performed: radical hysterectomy and pelvic lymph node dissection in 65 cases, complete hysterectomy in 7, extended hysterectomy in 2, supracervical hysterectomy in 2, and other type in 1 case.

TABLE VIII.—METHODS OF THERAPY IN 38 PATIENTS WITH STAGE IV LESIONS, 1952 TO 1957

Treatment	*No. of cases*
Cobalt rotation therapy	9
2 M.E.V. roentgenotherapy with opposing fields	2
Radium and 2 M.E.V. therapy	1
Exenteration	2
Palliative roentgenotherapy	20
Not treated	4
Total	38

TABLE IX.—COMPLICATIONS IN 65 PATIENTS TREATED BY RADICAL HYSTERECTOMY WITH NODE DISSECTION AND EXTERNAL ROENTGENOTHERAPY 1944 TO 1951

	Early	*Late*
Fatal	0	0
Major	6 Ureterovaginal fistula	1 Bladder neck obstruction 1 Stricture of ureter
Moderate	6 Operative shock 2 Paralytic ileus 1 Mechanical ileus 1 Pelvic abscess 3 Cystitis 2 Pyelonephritis	1 Mechanical ileus 5 Cystitis 2 Hydronephrosis

TABLE X.—TYPES OF OPERATIONS IN 142 CASES OF PRIMARY CARCINOMA OF THE CERVIX, 1952 TO 1957

Radical hysterectomy with node dissection and external roentgenotherapy	53
Radical hysterectomy and node dissection	64
Incomplete operation	12
Anterior exenteration	8
Total exenteration	2
Other	3
Total	142

Of the 65 patients treated by radical hysterectomy, 47 received postoperative external irradiation. The standard procedure was about a 3,500 roentgen tumor dose with 250 kilovolt radiation to the pelvis through four 10 by 15 centimeter portals over a 4 week period. The complications are shown in Table IX.

There were no operative deaths in this group. All 6 patients with operative shock responded well to transfusions. Both patients with mechanical ileus were treated conservatively by Miller-Abbott tube.

Of 6 patients with ureterovaginal fistulas, 2 have died of cancer and 4 are living without disease, there being no residual urologic disability in the survivors. The bladder neck obstruction was relieved by transurethral resection. The patient listed as having stricture of the ureter has, in addition, cystitis which is incapacitating. Late cystitis in 5 patients probably resulted from radiation therapy.

Complications in patients treated by operation, 1952 to 1957. From 1952 to 1957, 142 patients were submitted to operation. The distribution according to the International Classification is given in Table II and the type of surgical procedure in Table X. The incomplete operations were performed because of the extent of disease or for technical reasons.

Complications in patients treated by radical hysterectomy and node dissection. During this period, 1952 to 1957, the standard operation for surgically treated patients was radical hysterectomy and node dissection, 117 being treated in this way. A little less than half received postoperative external irradiation with doses to the pelvis of 3,000 to 6,000 roentgens administered in 1 month to 6 weeks. The complications developing in these 2 series, 1 with and 1 without postoperative roentgenotherapy, are shown in Tables XI and XII.

In the group treated by operation alone, there were 3 operative deaths and 12 major complications among 64 patients with stages I and II lesions. In the group of 49 patients with stages I and II lesions given postoperative irradiation, a fracture of the femur developed in 1, and in several late cystitis and proctitis and 2 cases of hydronephrosis developed, requiring operative intervention.

The proctitis, cystitis, and the hip fracture, in a patient receiving a 5,000 roentgen tumor dose by 250 kilovolt rotation therapy in 6 weeks, were probably attributable to irradiation. The 2 patients with ureteral obstruction requiring operative intervention received a 5,000 roentgen tumor dose by roentgenotherapy over a period of 4 to 6 weeks and, since the stricture developed 4 months after therapy, these may well have been caused by combined radiation and surgical scarring.

From these 2 series it appears that postoperative roentgenotherapy after radical hysterectomy may add somewhat to the late morbidity. However, in this series it was not evident that permanent damage had resulted except in patients who received 5,000 roentgens.

Pelvic exenteration. Eight anterior exenterations and 2 total exenterations were performed on 5 patients with stage II, 3 with stage III, and 2 with stage IV lesions. An analysis of these cases with the complications is presented in Table XIII.

The 1 death was due to radiation necrosis of the bowel, manifesting itself about 5 months after the administration of 5,000 roentgens through 15 by 15 centimeter portals by cobalt rotation therapy in 6 weeks to a patient who had undergone an anterior exenteration for a lesion classed as stage II but who was found at operation to have bladder involvement. Although only 3 complications and 1 death are reported in this group, there are only 3 of the 10 patients living 3 to 8 years without disease. The remaining 6 died of recurrent disease.

SUMMARY OF DATA ON THE EFFECT OF INCREASING THE DOSAGE OF ROENTGENOTHERAPY

A major change in the program for the therapy of cancer of the cervix in the 2 hospitals during the 15 year period under survey was the increase in roentgenotherapy dosage made possible by supervoltage apparatus. This increase was superimposed on an established radium technique originally designed to give what was believed to be the maximum dosage which would be tolerated by the rectum and bladder.

If one relates the complications to the amount of roentgenotherapy given, it appears that, with our radium techniques, injuries are more common in patients treated with more than 4,000 roentgens in a period of 4 to 6 weeks (Table XIV).

In the group managed by radium and roentgenotherapy there were 65 patients who received more than 4,000 roentgens to the pelvis. There were 4 deaths and 5 major complications. On the other hand, among 40 similar patients treated with less than a 4,000 roentgen tumor dose, there were only 2 major complications and 2 deaths, both unrelated to roentgenotherapy.

Similar differences were found in the group treated by extraperitoneal node dissection after radiation therapy. Of 39 patients in this group who received radium and more than 4,000 roentgens by roentgenotherapy to the pelvis, major complications developed in 14 and 2 died. Included in this group are 5 patients with stage I

TABLE XI.—COMPLICATIONS IN 64 PATIENTS WITH STAGE I AND II LESIONS TREATED BY RADICAL HYSTERECTOMY AND NODE DISSECTION WITHOUT POSTOPERATIVE IRRADIATION, 1952 TO 1957

	Early	*Late*
Fatal.....	1 Hemorrhage 1 Shock, transfusion reaction 1 Anesthesia	1 Death after repair of incisional hernia
Major.....	7 Ureterovaginal fistula 1 Combined ureteral and rectal fistula 1 Wound disruption	1 Retroperitoneal lymph accumulation 1 Gangrene of bowel 1 Incisional hernia
Moderate..	1 Pelvic abscess 2 Pyelitis with pelvic cellulitis, and pelvic thrombophletitis 3 Pyelitis and hydronephrosis 3 Pyelitis	1 Persistent hydronephrosis 1 Stress incontinence
Totals.....	21	6

TABLE XII.—COMPLICATIONS IN 49 PATIENTS WITH STAGE I AND II LESIONS TREATED BY HYSTERECTOMY AND NODE DISSECTION WITH POSTOPERATIVE ROENTGENOTHERAPY, 1952 TO 1957

	Early	*Late*
Fatal.....	0	1 Pulmonary embolus 6 months postoperative
Major.....	5 Ureterovaginal fistula 1 Wound disruption	1 Fracture of femur 2 Bilateral hydronephrosis requiring operative intervention
Moderate..	0	4 Hydronephrosis 1 Cystitis and hydronephrosis 2 Pyelonephritis 2 Proctitis
Totals.....	6	13

TABLE XIII.—EXENTERATION OPERATIONS FOR PRIMARY CARCINOMA OF THE CERVIX, 1952 TO 1957

	Total	*No. of patients with no post-operative roentgenotherapy*	*Complications*	*No. of patients receiving post-operative roentgenotherapy*	*Complications*
Stage II.....	5	3	1 Incontinence of urine following anterior exenteration	2	1 death secondary to radiation necrosis of bowel 1 hydronephrosis requiring secondary operation
Stage III.....	3	1	1 Hydronephrosis and nonvisualized kidney	2	0
Stage IV.....	2	2	0	0	0
Total.....	10	6	2	4	2

TABLE XIV.—RELATIONSHIP OF EXTERNAL ROENTGEN DOSAGE TO INCREASE OF INTESTINAL INJURY AND OTHER MAJOR COMPLICATIONS IN STAGES I AND II, 1952 TO 1957

	Over 4,000 roentgens to pelvic wall				*Less than 4,000 roentgens to pelvic wall*			
Treatment	*No. of cases*	*No. of deaths*	*No. of major complications*	*No. of major bowel necrosis*	*No. of cases*	*No. of deaths*	*No. of major complications*	*No. of major bowel necrosis*
Radium and roentgenotherapy.....	65	4	5	4	40	2	2	0
Radium, roentgenotherapy and lymph node dissection.....	39	2	14	3	14	1	3	0
Hysterectomy, lymph node dissection, and roentgenotherapy.....	40	1	8	1	8	0	1	0
Total.....	144	7	27	8	62	3	6	0

The tumor dosages were not calculated on 21 additional private patients and there were no injuries.

lesions of whom 4 suffered major complications and 1 died. Contrasted with the 39 receiving over 4,000 roentgens were 14 patients who received identical treatment except that they were given less than a 4,000 roentgen tumor dose. In this group were 3 major complications and 1 death, the latter a direct result of the surgical procedure.

In the group treated by radical hysterectomy and node dissection followed by over 4,000 roentgens of external irradiation there were 40 patients. The 1 fatality in this group was due to a pulmonary embolus 6 months after operation. There were also 8 major complications due to surgery, radiation, or a combination of these, but 2, a fracture of the femur and a bilateral ureteral obstruction requiring surgical intervention, developed 1 year after therapy. Both patients with these major late injuries had received more than 5,000 roentgens.

The problem of roentgenotherapy after such a major procedure as pelvic exenteration is of course a special one. However, there was 1 death due to radiation necrosis of the bowel in the exenteration series that followed a 5,000 roentgen tumor dose after an anterior exenteration for a stage II lesion.

DISCUSSION

After this survey of the complications in the management of 748 cases of cancer of the cervix at these 2 institutions, it appears that there has been a greater number of fatalities and severe complications in recent years. To determine the reasons for this is essential. In the radiation series there seem to have been 2 main factors: (1) the introduction of the pelvic node dissection after full radiation therapy and (2) the increase in dosage of roentgenotherapy. The recognition of these factors has resulted in certain changes in our routines.

In the patients in whom extensive operation and increased radiation were combined, these factors are of course additive. Preoperative irradiation makes the normal tissue less able to tolerate operation, and surgical treatment may render tissues more vulnerable to large doses of subsequent radiation. As a result of our experience with

operation performed after roentgenotherapy, postradiation node dissection has been abandoned in both hospitals.

Because it has become fairly obvious that treatment with more than 4,000 roentgens in addition to radium as given by our technique is hazardous, we have reduced the external irradiation in stages I and II to a maximum of a 4,000 roentgen tumor dose in 4 to 6 weeks with lead shielding in the center of the fields. In stages III and IV, however, when the radium dose may be reduced, it appears possible to administer a tumor dose of 5,000 roentgens or more to the pelvis.

An increase in surgical complications in recent years is perhaps less apparent. Nevertheless in the earlier period, from 1944 to 1951, there were 8 major complications in 65 patients, 12.0 per cent, with no deaths as compared with 21 major complications, 17.0 per cent, and 3 operative deaths, 2.0 per cent, in 113 of the later period. The increase in injuries may have been due to a less strict selection for operation in the later series, and it is noteworthy that all of the deaths occurred in patients in whom age or some other constitutional factor had increased the risk. It is our intent to return to a more careful exclusion of the bad risk case from surgical therapy.

With respect to the most discussed form of surgical complication, the ureterovaginal fistula, there has not been much change in incidence, which is 6 of 65 patients treated by radical hysterectomy in the 1944 to 1951 series and 13 of 113, 11.0 per cent, in the later period. Although such fistulas are much to be dreaded, they do not have the serious implication of the radiation injuries of the bowel, for, if the patient is cured of cancer, the urinary fistulas can be treated successfully. We have no permanent urologic "cripples" among patients operated upon for cancer of the cervix.

From our experience in the past few years, it is evident that there are complications from the radiation as well as from the surgical treatment of cancer of the cervix. Furthermore, there may be a radiation as well as a surgical mortality. Many of the radiation complications, however, may probably be eliminated by a better adjustment of the external radiation and radium dosages.

The hope that a higher cure rate may be obtained by subjecting patients to higher and higher dosages of external radiation appears to be sharply limited by the tolerance of normal tissues to these high dosages. Just as these tolerance dosages for radium applied by various techniques has gradually come to be known, so experience has helped adjust dosage with the new supervoltage methods.

SUMMARY

The cases of 748 patients with primary carcinoma of the cervix treated at the Francis Delafield and the Presbyterian Hospitals have been reviewed for complications. In recent years there has been a moderate increase in the number of injuries.

The reasons for this increase seem to be: (1) a less strict selection of patients for operation; (2) the combination of surgical therapy with radiation, as in the series treated by extraperitoneal node dissection after full radiation; and (3) the increase in dosage of external roentgenotherapy.

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THE EFFECT OF PREOPERATIVE ROENTGEN THERAPY UPON THE 10 AND 5 YEAR RESULTS OF THE SURGICAL TREATMENT OF CANCER OF THE RECTUM

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IN A PREVIOUS REPORT (1) we discussed the role of preoperative roentgenotherapy in the treatment of primary adenocarcinoma of the rectum and rectosigmoid. The study was based on an analysis of 1,786 untreated patients with this disease seen between 1939 and 1951 at the Memorial Center, New York. The 5 year results in the patients who had received no roentgenotherapy to the pelvis prior to standard radical resection were compared with those in the ones who did receive preoperative irradiation.

Unexpectedly, the 5 year results in these two series were comparable in all respects except in those patients whose tumors had metastasized to the mesenteric lymph nodes, namely, those considered under the Duke C classification. It appeared that these patients had benefited from the preoperative roentgenotherapy, because 37 per cent were alive 5 years after treatment, in contrast to 23 per cent of those who had not received any preoperative irradiation.

In the light of the statistically significant finding, the present study consists of an analysis extended to the 10 year survival level in the same patients, in order to determine a comparison with the 5 year results. In other words, the study investigates whether or not the beneficial effect of preoperative roentgenotherapy in patients with cancers of the rectum which have metastasized to mesenteric lymph nodes is as effective at the end of 10 years as it was at the 5 year survival mark.

A review of all cancers of the rectum treated by the members of the Rectum and Colon Service of the Memorial Center between 1939 and 1949 yielded a total of 770 cases available for this present analysis. This number constitutes all patients who had radical surgery with or without preoperative roentgenotherapy. It is understandably a smaller number than reported before, because at this time the years 1950 and 1951 cannot be included in a 10 year follow-up study.

The results are presented in Table I where they are listed under a breakdown of Duke's classification, roentgenotherapy versus no roentgenotherapy, and 5 versus 10 year survival rates. Both over-all survival rate and that corrected for determinates are given.

The relative number of patients receiving and not receiving preoperative roentgenotherapy is similar in each Duke's category. The indeterminates are those without disease when last heard from or who had died without evidence of cancer but from other causes less than 5 and then less than 10 years after treatment. The determinate survival figures exclude these patients.

The patients with tumors that have not metastasized to the mesenteric lymph nodes apparently do just as well, with or without preoperative roentgenotherapy, for their 5 and 10 year survival rates are approximately the same. On the other hand, of patients whose cancers had metastasized to lymph nodes, those who had received preoperative roentgenotherapy had a 37 and 27 per cent over-all 5 and 10 year survival rate, respectively, as compared to a 23 and 10 per cent

TABLE I.—COMPARISON OF RESULTS IN PATIENTS WITH AND WITHOUT PREOPERATIVE IRRADIATION

	Duke A		Duke B		Duke C		
	X-ray	*No x-ray*	*X-ray*	*No x-ray*	*X-ray*	*No x-ray*	*Total*
No. of patients	101	74	158	108	188	141	770
Incidence in series, per cent	23	23	35	33	42	44	—
5 year group							
Indeterminate, No.	15	7	11	11	13	9	66
Survivors, No.	74	55	103	71	69	33	405
Over-all survival, per cent	73	74	65	66	37	23	53
Determinate survival, per cent	86	82	73	77	39	25	58
10 year group							
Indeterminate, No.	6	6	14	10	2	8	46
Survivors, No.	54	43	74	49	50	14	284
Over-all survival, per cent	53	58	47	45	27	10	38
Determinate survival, per cent	68	70	56	56	30	11	43

survival, respectively, for the ones who had not received preoperative irradiation. In other words, these data indicate that the beneficial influence of preoperative roentgenotherapy on patients with cancers of the rectum which have metastasized to the mesenteric lymph nodes exists not only at the 5 year level, as was previously reported, but continues and becomes even more significant at the 10 year survival mark.

In summary, the following points may be stated:

1. Statistics on 770 surgically treated patients with primary adenocarcinoma of the rectum seen at the Memorial Center, New York, between 1939 and 1949 are reviewed. They were divided into those who did and those who did not receive preoperative roentgenotherapy.

2. Five year and 10 year survival rates are compared in these two groups according to Duke's classification of their resected specimens.

3. Whereas preoperative roentgenotherapy did not appear to affect the survival of patients with cancer that had not spread to the mesenteric lymph nodes, it definitely seemed to influence in a beneficial way the survival of patients with tumors with lymph node metastases.

4. The Duke C group of patients who had received preoperative irradiation had a 37 and 27 per cent 5 and 10 year survival, respectively. The Duke C patients not given preoperative irradiation yielded, respectively, only a 23 and 10 per cent 5 and 10 year survival.

On the basis of these findings, it is believed that preoperative roentgen irradiation is a worthwhile adjunct to the standard radical resections now universally employed for the treatment of cancer of the rectum.

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EDITORIALS

DIRECT APPROACH TO REPAIR IN PLASTIC SURGERY

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THE DIRECT APPROACH to repair in plastic surgery means fitting known surgical principles and procedures to the deformity. Construction or restitution of a feature or a part then becomes possible with the minimum number of operations, less pain and discomfort, and the least time lost for the patient in the hospital or between operations. Indirectness of thought and trying to fit the patient and his deformity into a favorite category of operation may invite the opposite.

The treatment of facial injuries is a good example of directness in the approach to repair. The term "compound facial injury" is a constant reminder that there may be injury to the underlying bony framework of the face after trauma, although the overlying contused, swollen, soft tissue might mask it at first glance. After roentgenographic confirmation, reduction is performed, as soon as the patient's general condition permits, by replacing those bones into proper position through the simplest means possible. Direct approach to the fragments and reversing the force causing the trauma have been made almost axiomatic by common usage. Union results after direct fixation with wire pins driven across the face by employing a cantilever effect from any stable point in the face. Direct wiring of facial fractures is done when possible through open soft tissues. In many instances, primary definitive repair of a compound facial injury gives the best possible restitution and may avoid later operations.

Patients with large burned areas, particularly the young or aged, cannot progress to eventual healing unless surgical debridement is followed directly by coverage with skin. Postmortem homografts supply an unlimited source of skin for temporary coverage, until the patient can withstand the transference of his own skin.

Burns of limited extent can be debrided, when they are first seen, and covered immediately with the patient's own skin for permanent healing. In a similar manner, rapid coverage of burned features and hands, after early debridement, avoids deep scarring, contractures, secondary resurfacing, and the necessity for further addition of skin.

Cleft lip repair remains a perpetual challenge to the plastic surgeon, as do all congenital deformities. A completely normal lip without scar is the objective. The final result, unfortunately, is never as good as the conscientious surgeon would wish, nor as the patient deserves. The best results are obtained by following simple, measurable markings on the lip and nose and concentrating on the details of repair. This direct approach can convert an acceptable into a superior effect.

Construction of an essentially normal appearing palate, where there has been a congenital cleft, is usually possible. Direct approach and an understanding of its action are more important, since there may be a

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problem of function. Closure and elongation, where necessary, of mobilized palatal soft tissue in one operation establish a normal mechanical and physiologic relationship. The nervous, muscular and vascular components are not disturbed. Indirect operations, such as on the posterior pharyngeal wall, are left for those instances in which the normal is impossible.

Total ear construction can be accomplished in three fundamental operations in which locally available tissue, free skin graft, and an armature of some sort are used. Silicone compounds seem to be the best nonliving material available for subcutaneous prostheses at the present time. Distant flaps used initially in total ear construction are a roundabout approach.

Directness of approach is equally important to the patient in operations performed to improve other features, such as the nose. It is unimportant whether the deformity is due to trauma or is a familial or racial characteristic. Discussion and demonstration lead to understanding with the patient preoperatively. The only limit to his complete satisfaction is what is possible surgically with his tissues.

Defects of the supporting framework of the face, or subcutaneous tissue, can be built up in one operation to the limit of the skin envelope. In addition, sometimes the skin can actually be stretched by successively larger subcutaneous implants. Similarly, fresh auto-implants are always best but may not be available or advisable, and substitutes are continually being sought. At present it appears that high polymer synthetics may prove of merit as substitution for any auto-implantation or homo-implantation.

Skin deficiency in an occasional instance may necessitate the use of a flap, but this expressionless addition is always a secondary consideration in the treatment of these conditions. The use of a flap primarily is an indirect approach and bends the needs of the patient to the training of the surgeon.

Extensive bone and soft tissue loss such as may occur in a gunshot wound of an extremity may sometimes be healed by dressing the wound in a free graft. If a bone graft is later necessary for the restoration of function, the bulk of a flap is necessary for bony union. An abdominal flap with a broad base can be directly applied to the defect and avoid the delay of elevation and preparation in stages.

A permanent pedicle blood-carrying flap can be used for direct application and will increase the vascular supply of an area. Increased blood supply is always desirable in such conditions as irradiation burns in which it is characteristically poor. Other flaps remain dependent on the recipient area for their blood supply.

Normal replacement of tissues lost by trauma or congenitally absent would be perfection. Perfection in plastic surgery, as in all other things, is ever sought, but seldom attained. The best results are then the product of the plastic surgeon with uncommon common sense, consistently following fundamental surgical principles, never tempted to fit a deformity, traumatic or congenital, into a favorite category of repair.

THE NEED TO RE-EMPHASIZE THE PRINCIPLES OF ASEPSIS

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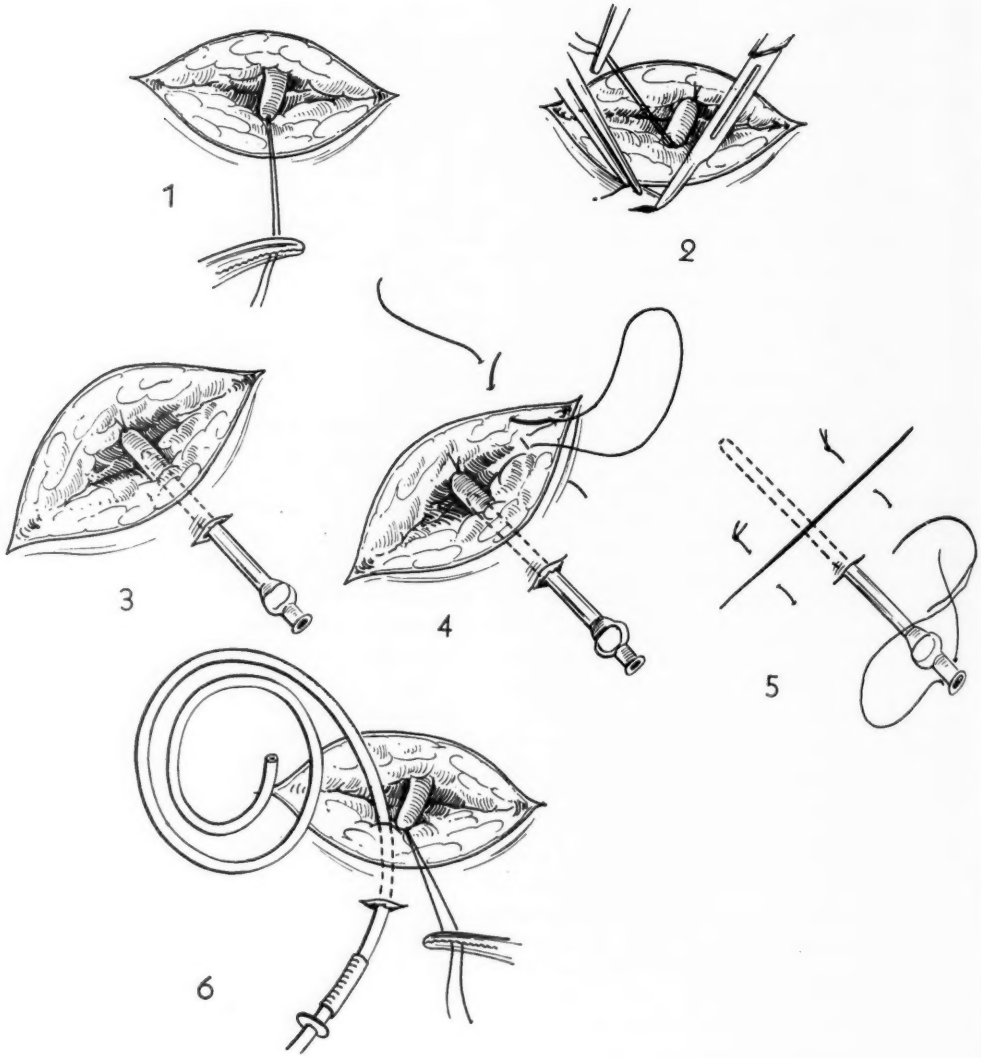
IN ALMOST EVERY BASIC COURSE of surgical teaching, stress is put on the so-called surgical conscience. But are these precepts actually followed by the practicing surgeon? Are the surgical teachers practicing their own preachings?

Observing the operating room suites of the teaching hospitals, one sees so many breaks in technique that one wonders whether or not we are giving lip-service to this essential precept. On a recent trip, the surgical section of a newly constructed university hospital was observed and it was the acme of efficiency and safety. All of the precautions of modern hospital architecture were in evidence. Yet there was an orderly without cap and without mask polishing the floor outside of one of the major operating rooms. The surgical team surrounding the operating table was gowned and double masked; yet every one of them was wearing shoes soled with nonconductive rubber. While the famous surgeon was operating, the internist who had been following the patient put his head through the door and conversed with the surgeon. He had no mask over his face, no cap covering his scalp, and he was protected only by a white coat worn on hospital rounds. The surgeon's glove had a hole in the left index finger, which any observer could plainly see. These were some of the gross errors which were observed by students being indoctrinated with a surgical conscience.

Nearly every hospital has been advised to have an asepsis committee or some group whose efforts are devoted to reducing the incidence of surgical infections. The literature is becoming crowded with scientific studies on wound infections. The staphylococcus is being followed through laundries, dishwashers, airconditioning ducts, and airvents. Patients are being plied with antibiotics and plagued with isolation rooms. Chemicals are being added to everything from dishwater to nurses underwear to kill bacteria. Yet the simple rules of aseptic technique are unobserved.

Sampling of new surgical gloves has shown that an appreciable percentage have holes in them, holes large enough to transmit bacteria. Studies have shown that in each major operation, at least one member of the operating team has a hole in one of his gloves. Others have found that the inside of the rubber glove frequently is contaminated with pathogenic staphylococci and other pathogens, even though the surgeon has scrubbed in approved fashion. Yet surgeons will continue to wear a glove obviously torn.

Asepsis committees are valuable. Epidemiologic studies are important. But most important is the redevelopment of the surgical conscience, meaning employment of all of the safeguards which modern surgical science has given us. The responsible surgeon has the obligation to require every member of the staff to protect his most valuable asset—his patient.



FIGS. 1 to 6.

Modified Technique for Intravenous Cannulation.—H. A. F. Dudley.

THE SURGEON AT WORK

MODIFIED TECHNIQUE FOR INTRAVENOUS CANNULATION

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EXPOSURE AND CANNULATION of a vein for intravenous therapy is now not common but may still occasionally be required in children or when veins are difficult to enter with a needle. In such cases it is usual to insert the cannula through the incision made to expose the vein. Accurate skin approximation is thus rendered impossible and healing may be delayed. The entry of bacteria is probably also facilitated and may contribute to the increasing incidence of infection associated with intravenous therapy, according to Hassall and Rountree, McNair and Dudley, and Moncrief. The modification herein described is a minor one and may well have been widely used, but I have been unable to find any previous description.

TECHNIQUE

Metal cannulas which are of uniform bore or the appropriate size of nylon or polythene catheter are used. The vein is exposed in the usual manner and ligated distally with fine catgut (Fig. 1). A small scalpel blade is used to make a nick in the distal skin flap about 0.75 centimeter beyond the incision (Fig. 2). The cannula is inserted through the puncture and on into the vein in the usual manner (Fig. 3). The proximal ligature is tied sufficiently tightly to prevent leakage but not so firmly that the cannula cannot be slid slightly up and down the vein. The skin incision is accurately closed with 2 or 3 vertical mattress sutures of fine silk (Fig. 4). A further stitch (Fig. 5) is then inserted by taking a generous bite of skin 1.5 centimeters from the distal aspect of the incision. This ligature is tied to form a short mesentery and is then knotted firmly around the cannula (Fig. 5). It is this stitch that supports the cannula, prevents its accidental withdrawal, and deters a restless patient from pulling it out. If a length of plastic tubing is used, it is most easily inserted by first drawing it through the stab as shown in Figure 6. It is then led into the vein and any excess pulled back.

Removal of the cannula is carried out by cutting the anchor stitch and pulling the cannula firmly but gently. The incision is not disturbed.

The technique has been used with great satisfaction for 3 years and is now routine when cannulation by exposure of the vein is indicated.

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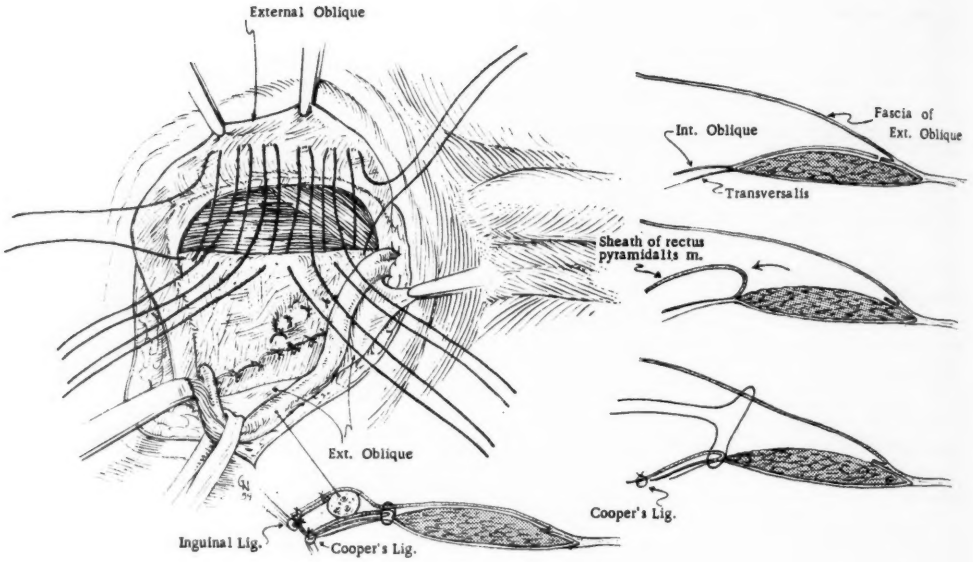

FIG. 1.

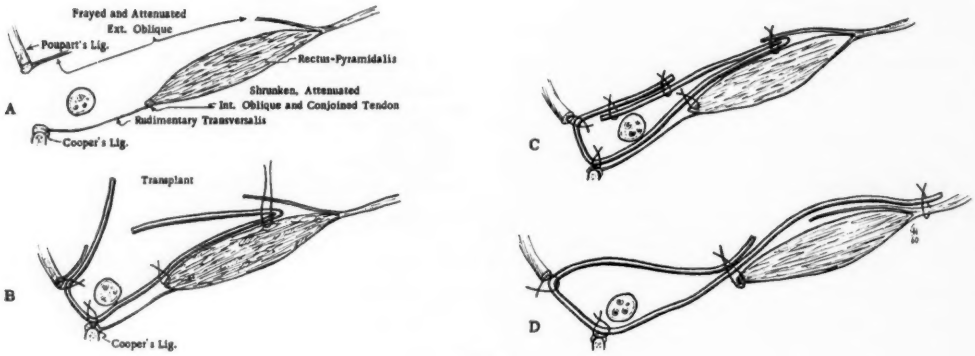

FIG. 2.

(*Legends on facing page.*)

A Basic Concept in the Use of the Rectus-Pyramidalis Sheath and Transplants in the Repair of Hernias.—Edgar J. Poth.

A BASIC CONCEPT IN THE USE OF THE RECTUS-PYRAMIDALIS SHEATH AND TRANSPLANTS IN THE REPAIR OF HERNIAS

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A RECENT ARTICLE by McVay and Chapp recalled a technique which I have used for 25 years and which has not, to my knowledge, been reported in the literature. The procedure is so simple and appears so obvious that it is hard to believe that it has not already been described. If this belief is true, however, the method is so little known that a description is justified. If it has been presented previously, priority will be acknowledged forthwith.

Bloodgood advocated the use of the rectus muscle, different in detail but similar in principle to the method which was originally proposed by Woelfler for the repair of inguinal hernias. Halsted had misgivings about suturing the rectus muscle to the shelving edge of Poupart's ligament for fear that it would be pulled off. Therefore, a counter, relaxing incision was made into the anterior sheath of the rectus extending downward to include the pyramidalis sheath, thus allowing the sheath to be slipped laterally for suturing the conjoined tendon to the shelving edge of Poupart's ligament. The lateral edge of the cut rectus sheath would then lie under and in direct contact with the external oblique sheath and by sending out pseudopodia would become attached to the nether surface of the external oblique, and thereby repair the medial defect and reclose the rectus space.

He also turned the sheath over like a pedicle and sutured the cut edge to Poupart's ligament if the conjoined tendon was too attenuated to reach. Berger, in 1902, described a similar procedure which had the advantage of giving sufficient length of sheath to permit suturing without tension. Halsted used this technique for the first time in 1899 while operating upon a classmate, "... for the first time, a part of the aponeurosis covering the right rectus muscle to close the lower part of the right inguinal canal. I felt compelled in this case to resort to some such measure, for the internal oblique was fatty and attenuated to a degree not very often seen by us, and the rectus muscle did not seem to

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FIG. 1. Illustration shows rectus-pyramidalis sheath being used for repair of hernia when the transversalis fascia and aponeurosis are thinned out or the conjoined tendon is attenuated. The rectus-pyramidalis sheath is turned back like a pedicle. The inferior epigastric artery and vein are divided. The pedicle is first sutured about 15 millimeters back from its cut edge to Cooper's ligament and then at the cut edge along the entire length of Poupart's ligament. The medial, rolled edge of the pedicle is then sutured with moderate tension to the under surface of the medial flap of the external oblique, where it becomes fused, firmly anchoring the pedicle along its medial extremity and closing the rectus-pyramidalis space.

FIG. 2. Repair of hernia with fascial or artificial transplants following practically complete destruction of the external oblique, the internal oblique, and the transversalis structures. The transplant substitutes for these structures. It is preferably an autograft of fascia lata. The graft is centered over the defect. It is sutured to Cooper's ligament first and then along the remnant of Poupart's ligament or in such a manner as to simulate this structure. Next, the transplant is brought behind the cord to simulate the transversalis fascia and aponeurosis so it may be sutured to the lateral edge of the attenuated conjoined tendon or rectus-pyramidalis sheath anteriorly at the desired tension. Subsequently, the transplant is sutured to the under surface of the rudimentary medial flap of external oblique. The transplant can be carried to the midline fascia if the external oblique is completely absent. The medial and lateral flaps of the transplant are then sutured over the cord by imbrication to simulate the external oblique. Another modification is illustrated in "D." The order of suturing in this instance is: (1) to Cooper's, (2) to Poupart's, and (3) the lateral flap is brought anterior to the cord and sutured at the desired tension to the attenuated conjoined tendon and/or the lateral edge of the rectus-pyramidalis sheath together with the segment of transplant which passes posterior to the cord and simulates the transversalis fascia and aponeurosis, and, finally, the transplant is carried as far medially as necessary and even to the midline structures if necessary. Interrupted, nonabsorbable sutures, not of wire, are used throughout.

promise so much as its fascia did. This patient was a college-mate of mine and for this reason I wished, perhaps, more than ever, to be very sure of the result. One year ago (three years postoperative) I examined this patient very carefully and was gratified to find as solid a closure as one could desire. I considered the result as perfect as any that I had seen."

METHOD

Unfortunately, recurrences were more frequent with use of the rectus sheath pedicle than with the relaxing maneuver. Failures were the result of defects which developed medially and most likely were due to the anatomic arrangement in which practically all of the fibers of the transversalis fascia and aponeurosis were anterior to the rectus muscle at this level. This arrangement resulted in the pedicle of the rectus-pyramidalis sheath being anchored medially at the lateral edge of the rectus muscle to the very weak posterior structure and suspended superiorly and inferiorly in a hammock slinglike fashion to the strong anterior rectus and pyramidalis sheaths at both ends of the incision.

If the medial, rolled edge of the inverted rectus-pyramidalis sheath is sutured to the under surface of the external oblique fascia, the weak, unsupported medial edge would be strengthened, the length of the rectus-pyramidalis pedicle preserved, and the rectus space closed. This procedure has been used successfully since 1934. Originally, the lateral edge of the pedicle was sutured regularly to the shelving edge of Poupart's ligament for the repair of all recurrent and direct hernias.

Since the descriptions of Anson, McVay, and Morgan calling attention to the importance of Cooper's ligament, the site of suturing was changed by placing an additional 3 to 4 interrupted sutures into this ligament. The pedicle is sutured about 15 millimeters medial to its lateral edge to Cooper's ligament posteriorly, and then the lateral cut edge is further sutured to Poupart's ligament anteriorly, along its entire length. This modification gives added support to Poupart's ligament and closes the space between Poupart's and Cooper's ligaments completely to reinforce and extend Gimbernat's ligament. This method is especially important in the repair of a femoral hernia.

RESULTS

The procedure has been most successful. There have been no recurrences medially. Recently, a recurrence developed directly through the central portion of the sheath by separation of the fibers. Secondary repair was successfully performed by resuturing the two leaves of the pedicle by slight imbrication. These same principles can be applied when using fascial or inert transplants as substitutes for both the external oblique fascia and the rectus-pyramidalis pedicle by anchoring them medially to the under surface of the external oblique and to the anterior rectus sheath and laterally to Cooper's and Poupart's ligaments if extensive destruction of the normal structures has occurred (Fig. 2).

CONCLUSION

Since the procedure has been tested thoroughly over a long period it can be confidently recommended.

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THE TREATMENT OF POSTOPERATIVE PULMONARY ATELECTASIS WITH INTERMITTENT POSITIVE PRESSURE BREATHING

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INTERMITTENT positive pressure breathing on inspiration with nebulizing of bronchodilators and detergents has been used with good effect in chronic bronchitis with emphysema, bronchial asthma, and bronchiectasis. Recently, its use has been advocated for prophylaxis and therapy of postoperative pulmonary atelectasis. Because no controlled study had been made to prove its efficacy in this condition, the present investigation was undertaken and carried out to observe its effectiveness.

METHOD

One hundred consecutive patients undergoing upper abdominal surgery were included in this study during the winter, spring, and summer of 1958 and 1959. Alternate patients were treated with intermittent positive pressure on inspiration with oxygen and nebulization of 0.25 cubic centimeter of isuprel in 1 to 200 dilution with 2 cubic centimeters of alevaire. A mine safety appliance ventilator supplied the positive pressure on inspiration. The first treatment was given on the evening of operation and was followed by 2 to 3 treatments daily for 3 days. The treatments each lasted 5 to 10 minutes and were given under supervision of a trained technician at a pressure of 10 to 15 centimeters of water on inspiration. In addition, all patients were treated by early ambulation, deep breathing and coughing were encouraged, and patients were moved from side to side in bed. Antibiotics were used prophylactically in a minority of patients. Nasogastric suction was routinely employed postoperatively. Tight abdominal binders and excessive use of narcotics were avoided. Chest roentgenograms were taken of all the patients in the erect position in the x-ray department on the first and fifth postoperative days.

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The treated and control group of patients were similar as to sex distribution and age. Anesthesia was also the same, being cyclopropane with endotracheal intubation, preceded by induction with sodium pentothal intravenously, and accompanied by injections of succinyl choline. There was 1 patient in each group operated upon under spinal anesthesia. One patient in the treated group received local block as the sole anesthesia. The duration of operation was similar in both groups. Cholecystectomy with and without common duct exploration was performed in 75 patients and gastric surgery in 17. Operations on ventral hernias, exploratory laparotomies, and partial colectomy were performed in the remaining 8 patients. These various operations were evenly divided between the treated and control series. Three patients in the treated group had pre-existing chronic bronchitis or asthma. Only 1 patient in the control group had a similar disease.

RESULTS

The presence or absence of atelectasis was determined solely by chest roentgenograms. Lobar or multilobar atelectasis, patchy or segmental atelectasis, and platelike atelectasis were the 3 types demonstrated. The most common was platelike atelectasis. Fifty patients were treated with intermittent positive pressure breathing with bronchodilators and detergents. Platelike atelectasis developed in 14, segmental atelectasis in 10, and lobar atelectasis in 1. Fifty patients received no intermittent positive pressure breathing, bronchodilators, or detergents. Platelike atelectasis developed in 20, segmental atelectasis in 4, and lobar atelectasis in 2. There was no apparent advantage of intermittent positive pressure breathing in prophylaxis against postoperative atelectasis. The 50 patients treated with routine postoperative management of early

ambulation, frequent change of position, coughing, and deep breathing did as well as the specially treated group.

Atelectasis developed in 48 patients on the first postoperative day. Of the 22 patients treated with intermittent positive pressure breathing, 13 showed clearing. Three patients manifested atelectasis for the first time on the chest roentgenogram taken on the fifth postoperative day. These complications all occurred in the patients treated with intermittent positive pressure breathing. In 16 of the 26 patients without intermittent positive pressure breathing, the atelectasis was cleared. Again there appeared to be no difference in the rapidity of clearing of atelectasis once established in these 2 groups.

CAUSE OF POSTOPERATIVE ATELECTASIS

The cause of postoperative atelectasis is considered to be bronchial obstruction due to secretions within the lumen. Air behind the obstructed bronchus is absorbed by the circulating blood and no air is replenished because of the block. An airless plate, segment, lobe, or lung results, depending upon the site of obstruction. This is the immediate cause of postoperative atelectasis and is agreed upon by most investigators of the subject.

The cause of the accumulation of bronchial secretions postoperatively is the relative immobility of the diaphragm and intercostal muscles due to the trauma of surgery. The hypoventilation of the lung interferes with the normal removal of bronchial secretions. Cough is also interfered with by the splinting of the diaphragm. Other factors have an effect by potentiating the splinting of the diaphragm and intercostal muscles or the production of bronchial secretions. Prolonged immobility, tight chest and upper abdominal binders, and excessive use of narcotics favor postoperative atelectasis by accentuating the splinting action. Recent respiratory infection, chronic bronchitis, and bronchial asthma predispose to accumulation of sputum by increasing its production.

Bronchial secretions or diaphragmatic splinting has been emphasized as the chief cause of postoperative atelectasis. Among those who incriminate diaphragmatic splinting is Pasteur who first described lower lobe atelectasis after postdiphtheritic diaphragmatic paralysis and its similarity to postoperative atelectasis. He concludes:

> I have endeavored to place before you the reasons which lead me to conclude that under certain conditions an active collapse of the lung takes place which may lead to entire deflation of one or more of its lobes. It is generally caused by paralysis of the muscles which are distenders of the lungs—the diaphragm and the intercostals—but I have also shown that there are strong grounds for believing that reflex inhibition of diaphragmatic movement may lead to the same result and that this observation may throw some light on the nature of postoperative lung complications.

Coryllos, a believer in "no bronchial obstruction, no atelectasis," describes the sequence of events as follows:

> After operation, especially the upper part of the abdomen, and this independently of the anesthesia used, general, local or spinal, an immobilization of the thoracic cage occurs, the vital capacity is decreased and the means of defense of the lung are impaired. This impairment is increased by the postoperative posture and narcotics. A stasis of bronchial secretions in the bronchial tree follows, producing an irritation of the bronchial mucosa, which responds by more secretion. A bronchiolitis occurs, which is due to the more or less infected stagnating secretions.
>
> This in turn leads to atelectasis.

King and Brock place chief emphasis on purulent bronchitis as the cause of postoperative atelectasis but do not explain the mechanism of its formation. Baker and coworkers stress the formation of viscous secretions with increased mucus as the fundamental cause of postoperative atelectasis. Maier and Kurzweg believe that blood stasis occurs in the dependent parts of the lungs, causing increased fluid to accumulate in the bronchioles, leading to atelectasis. De Takats and associates stressed vagal reflex changes initiated by tension on the abdominal viscera, leading to bronchial spasm and hypersecretion. Palmer and Selick list 24 factors which lead to deficient expulsive mechanism, reduction in bronchial caliber, and change in bronchial secretions. These in turn produce retention of sputum which is the immediate cause of atelectasis.

INCIDENCE

The incidence of postoperative atelectasis was 51 per cent in the 100 patients reported here. The atelectasis was chiefly platelike or segmental; lobar atelectasis occurred in only 3 patients. The diagnosis of atelectasis was made entirely by roentgenograms taken with the patient in the upright position. Other studies using routine roentgenograms postoperatively for diagnosis have shown similar high incidences after

upper abdominal surgery. Rudnikoff and Headland, routinely taking roentgenograms of cholecystectomy patients on the fourth postoperative day, found 28 of 40 patients or 70 per cent to show atelectasis. Stringer found 13 of 55 patients after partial gastrectomy to show atelectasis by routine postoperative chest roentgenograms, an incidence of 24 per cent. Muller and associates found various degrees of atelectasis by routine roentgenograms in 18 of 25 patients after upper abdominal surgery. Of 343 patients after cholecystectomy, Thoren found pulmonary complications in 104 by routine chest roentgenograms, an incidence of 30 per cent. This figure included his treated and untreated patients.

The incidence falls precipitously when chest roentgenograms are not taken routinely. Dripps and Deming found only 5.5 per cent of pulmonary complications after upper abdominal surgery in 1,240 patients. Routine roentgenograms were not employed in this study. There is a further drop in frequency when all types of surgical procedures are studied, again without routine chest roentgenograms. Eliason and McLaughlin reported an incidence of 1.38 per cent in all types of surgery. Baugh reported 1.03 per cent of pulmonary postoperative complications in 1,833 major surgical cases, again without routine chest roentgenograms.

CLINICAL SYMPTOMS AND SIGNS

Symptoms of pulmonary atelectasis depend upon the extent of the involvement. Platelike atelectasis consisting of minimal streaks of density produced no symptoms. Multiple plate atelectasis with a thickness of 3 to 4 millimeters was associated with dyspnea on exertion in a few instances. Segmental atelectasis was usually asymptomatic; in a minority slight dyspnea and cough were present. Lobar atelectasis was usually associated with the symptoms of cough productive of sputum, dyspnea, and chest discomfort.

After the usual cholecystectomy or subtotal gastrectomy, fever was usually present, rising no higher than 101 degrees F. and lasting no longer than 2 to 3 days. The presence of platelike or segmental atelectasis had no effect upon the febrile course. One patient with multilobar atelectasis had a fever above 101 degrees F. for 1 day. The other patients with lobar collapse were entirely afebrile. The physical findings of dullness to percussion, diminished breath sounds, and rales were heard at the lung bases in the majority of patients after upper abdominal surgery. This finding indicated elevation of the diaphragm and did not necessarily signify atelectasis. At times, bronchial breath sounds were also heard. Platelike and segmental atelectasis could not be diagnosed by physical findings and required roentgenograms for confirmation. Lobar atelectasis usually produced a mediastinal shift which could be recognized on examination. Loud rhonchi were heard in the patients with lobar collapse and in a few with segmental collapse. This is a highly characteristic physical finding of major atelectasis. Brock describes it as a "fruity" cough and found it in most cases of postoperative atelectasis. Haight and Ransom consider rhonchi as the earliest finding of atelectasis, often preceding other evidence of collapse.

ROENTGENOGRAPHIC FINDINGS

The chest roentgenogram taken on the first day after upper abdominal surgery usually showed an elevated diaphragm with some subphrenic air. The diaphragm showed greater elevation on the right side after cholecystectomy; the diaphragm was higher on the left side after subtotal gastrectomy. The lung bases showed increased bronchovascular markings. These changes were considered normal postoperative findings. The presence of plate atelectasis, even of minimal degree, was classified as postoperative atelectasis. This occurred in 34 cases, was usually present on the first postoperative day, and often disappeared on the fifth postoperative day. The thin linear shadows were usually multiple and horizontal in the lower half of the lung fields. A few occurred in the upper half of the lung fields and ran a diagonal course toward the hilum. There was no shift of the mediastinum, since many of the shadows were bilateral and the majority were minimal. Plate atelectasis was considered to be caused by the same factors which cause massive atelectasis; namely, retention of bronchial secretions associated with pulmonary hypoventilation and impaired cough, as Fleischner and associates have indicated. The airways which are blocked are considered to be the small bronchioles. Postmortem examination has shown the atelectatic areas to be associated with small bronchi occluded by secretion. The platelike atelectasis always extends to the

pleural surface but never crosses interlobar fissures. The factor of bronchial constriction also plays a part, since platelike atelectasis may disappear temporarily during deep breathing or on a Valsalva maneuver.

Segmental atelectasis was more difficult to define, since it occupied the area between platelike and lobar atelectasis. Most of the patients with this diagnosis had a diffuse density which appeared to be segmental in extent. A few had mottled infiltration of segmental extent. This has frequently been called lobular or patchy atelectasis. It has also erroneously been labeled as bronchopneumonia or pneumonitis. Segmental atelectasis is considered to be due to a block by secretions in the branch bronchi leading to the segments of the lung.

Massive atelectasis is considered to be synonymous with lobar or multilobar atelectasis. The roentgenogram is characteristic, with diffuse density occupying an entire lobe or lobes and associated with a shift of the trachea, heart, and diaphragm to the affected side. The block is considered to be in the lobar bronchus or main-stem bronchus. In the majority of instances the obstruction consists of mucoid, viscid secretions rather than a mucus plug.

THERAPY

Prophylactic therapy is directed against the accumulation of bronchial secretions and against the hypoventilation and ineffectual cough. Delay of surgery is of great importance when a respiratory infection, even of mild degree, is present. One patient in our series in whom a multilobar atelectasis developed had a mild cough a few days before surgery. Ravdin and Kern as well as Brock have emphasized this danger of operating in the face of a respiratory infection. Patients suffering from cigarette bronchitis should cease smoking for some weeks prior to operation. The presence of chronic bronchitis with emphysema, bronchiectasis, or bronchial asthma is an indication for the preoperative use of intermittent positive pressure on inspiration with nebulized bronchodilators and detergents. Antibiotics are also of value under these circumstances.

Intermittent positive pressure breathing with bronchodilators was employed by Motley and Tomashefski in therapy of pulmonary fibrosis and emphysema. Its favorable effect in chronic bronchitis, bronchiectasis, and asthma was confirmed by Smart and coworkers, Trimble and Kieran, and Farber and associates. The favorable effects were considered to be due to dilatation of the constricted bronchioles, improved ventilation of the lungs, and consequent penetration of the bronchodilators to previously inaccessible areas of the lungs. Its use preoperatively and postoperatively was suggested by Jones, Rudy and Crepeau, and Noehren and associates. Rudy believed that it was especially indicated in patients who could not be "coughed," such as postherniorrhaphy patients, in patients who could not be ambulated, and in those with chronic pulmonary disease. The use of nebulized bronchodilators without intermittent positive pressure breathing is said to be as effective. Palmer and Selick found that this form of treatment along with postural drainage was effective in the prophylactic treatment of postoperative atelectasis.

During the period of anesthesia, prophylaxis consists of avoiding hypoxia and hypercapnia. Immediately after operation, the removal of tracheobronchial secretions is mandatory. Greene and Berkowitz recommended tracheobronchial aspiration simultaneously with vigorous coughing postoperatively in patients with a "wet" or "self propagating" cough. Brown advised postoperative bronchoscopic aspiration in poor risk patients.

In the postoperative period, prophylaxis depends chiefly on the encouragement of the patient to cough, as pointed out by Haight and Ransom. The physician should support the patient's incision and strongly urge the patient on to vigorous coughing. This is best done with the patient lying on his side. Frequent turning of the patient from side to side and deep breathing exercises are also indicated. Early ambulation and avoidance of constricting dressings and excessive use of narcotics and sedatives are also helpful. There does not appear to be any necessity for the routine use of bronchodilators and detergents by aerosol with or without intermittent positive pressure breathing. However, in patients with chronic bronchial conditions it is wise to employ them as well as antibiotics. Baker and associates advocated sodium iodide intravenously in the postoperative period because they believed that viscid bronchial secretions with increased mucus was the fundamental cause of atelectasis. Their results were excellent, 100 consecutive surgical patients having no pul-

monary complications. Davidson believed that painful surgical incisions with splinting of the diaphragm and intercostals were the basic causes of postoperative atelectasis. He blocked the intercostal nerves with benzocaine and urethane and as a consequence achieved excellent results in prophylaxis of postoperative atelectasis.

Curative therapy of postoperative atelectasis consists chiefly of encouraging the patient to cough while using the lateral position and supporting the incision. If this measure fails to clear the atelectasis as demonstrated by physical or roentgenographic findings, tracheobronchial aspiration with a rubber catheter should be employed. If atelectasis still persists after this maneuver, bronchoscopic aspiration should be carried out. In our series, platelike atelectasis did not require any special therapy other than routine postoperative care of encouragement to cough, turning from side to side, deep breathing, and early ambulation.

It is of interest that almost every specialized procedure used in the prophylaxis of postoperative atelectasis has met with signal success. Carbon dioxide inhalation was long considered of great benefit; breathing exercises appeared to be a cure-all. Postural drainage with bronchodilator aerosols benefited patients greatly. Intravenous sodium iodide prevented all postoperative atelectasis. Local anesthesia to the intercostal nerves worked effectively. Tracheobronchial aspiration postoperatively appeared to solve the problem of postoperative atelectasis. Using intermittent positive pressure breathing with aerosols appeared to be the answer. Noehren states:

> Most suggestions for the improvement of postoperative management of patients have demonstrated improvement in results, and the common denominator of each of these appears to be closer attention to the patient postoperatively. This factor alone will often be sufficient without any of the additions, mechanical or otherwise. Perhaps the success with intermittent positive pressure breathing on inspiration has been on the same basis.

CONCLUSION

Postoperative atelectases occurred in 51 of 100 patients after upper abdominal surgery. These included 3 lobar, 14 segmental, and 34 platelike types of atelectasis.

Routine intermittent positive pressure breathing on inspiration with bronchodilator and detergent aerosols did not prevent the occurrence of postoperative atelectasis nor accelerate its clearance in patients with a normal bronchial tree. This therapy is chiefly indicated preoperatively and postoperatively in patients with chronic bronchial disease.

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PETER THE GREAT AND RUSSIAN MEDICINE

ROBERT M. GOLDWYN, M.D., Boston, Massachusetts

DURING the 53 years of his life and the 35 years of his reign, Peter I, better known as Peter the Great, displayed remarkable energies for learning, social reforms, empire building, profligacy, and cruelty. An unpredictable cyclone of emotions, this man once wept with pity over the dead body of an unknown child, yet, years later, had his own son killed by torture.

Born in Moscow in 1672, Peter was soon exposed to the medical care of the court physicians who treated his epileptic fits with the same fervor they had shown in dealing with a similar ailment in his half brother Ivan. One of their choice remedies was the "interior and wings of a magpie" (11). Acknowledging a possible psychogenic factor, some historians have traced the onset of these convulsions to an occasion in Peter's tenth year when he witnessed a rebellious mob hacking to pieces his uncle and his best friend. Throughout his childhood, he had a morbid fear of the dark, and only the presence of a male servant sleeping in the same bed could calm him. In 1685 he almost died of smallpox.

The short reign of a feeble elder stepbrother Theodore III (1661–1682), a co-Tsarship with a tonguetied half brother Ivan V (1666–1696), and the stormy regency of a ruthless half sister Sophia (1657–1704) preceded his complete accession to the throne. To stop the much publicized Bacchanalia of her 16 year old son, Peter's mother hastily arranged his marriage to the beautiful but slow-witted Eudoxia (1669–1731). Soon tired of his wife, he dispatched her with his ill-fated son Alexis (1690–1718) to a monastery. Peter was then free to devote his talents to his goal of making Russia a first class modern power. Having recognized that his country lagged well behind the Western European nations in the arts, the sciences, and technology, he decided to learn for himself by traveling and he became the first Tsar to leave Russia. Usually disguised as a simple workman or student, he studied gunnery at Königsberg, shipbuilding at Zaardam, engraving in Amsterdam, and anatomy in Leyden—with the renowned Hermann Boerhaave (1668–1738) and Frederick Ruysch (1638–1731). Ruysch had perfected a method for preserving specimens by injecting the blood vessels with an arsenic compound which solidified upon cooling. Impressed with the preserved beauty and accurate detail of the work, Peter bought the entire anatomic museum for $75,000 and Ruysch's secret of embalming for $25,000. The fame of Antony van Leeuwenhoek (1632–1723) and his microscope had reached Peter and he arranged a visit with him in Delft. Incredulously, he watched the circulation in the tail of an eel and later ordered a microscope from the modest, observant Dutchman.

In an effort to gain medical knowledge and to raise medical standards within Russia, Peter went further. Between 1695 and 1698 he imported 75 foreign physicians. Before that time there were no qualified Russian doctors in Russia and only about 35 foreign medical men. On a grand scale Peter organized the translation of important foreign scientific and nonscientific writings. Throughout his kingdom he announced

From the Surgical Service, Peter Bent Brigham Hospital, Boston.

that any qualified student wishing to study medicine would be sent abroad at the Tsar's expense. Postnikov, a son of a secretary of state, was one of the first to go. He went to Padua and returned in 3 years with doctorates in philosophy and medicine. Besides practicing medicine, Postnikov went on several important diplomatic missions as an interpreter.

On 25 May, 1706, a solid foundation for Russian medicine was laid: the Gofs Hospital in Moscow, the first true hospital in Russia, came into being. It was modelled after the Greenwich Hospital in England which Peter had seen in 1698. He wisely realized that the basic unit of Russian medicine would be the teaching hospital and, therefore, constructed facilities for the instruction of medical students. He imported Nicholas Bidloo (?–1735) from Holland to be court physician (Liebmedik) and later to head the Medical-Chirurgical Hospital and School. Only by 1712, however, could Peter generate enough enthusiasm among students to fill the 50 places at the medical school. The funds for this medical center were obtained by force from the Church. Constructed of wood and susceptible to fires, it was a costly institution which the Church reluctantly supported.

In 1701 Peter embarked upon a prolonged but eventually successful war with Sweden to obtain an ice-free Baltic port, later Saint Petersburg, for the new navy which had been built entirely under his supervision and partly with his own hands. To care for the mounting war casualties, he created, in 1706, the first military hospital and placed it under the control of civilian physicians. He also built a hospital for foundlings which was financed by deductions from the wages of his officers. Later, in 1716 and 1720, he reorganized the army and navy medical services by making new posts of surgeon-general, physician, and medical officers for each division and a surgeon for each regiment. Having recognized the importance of drugs in the treatment of disease and also the necessity for the public to have access to certified remedies, he created the first public dispensaries in Saint Petersburg and others in Kazan, Reval, Riga, and Moscow.

Peter's two court physicians were Bidloo and Robert Erskine, the latter in charge of the state dispensaries. Bidloo was Peter's trusted confidant and advised him in affairs diplomatic as well as medical. He designed the botanical gardens of Moscow and had reprinted his father's well known book, *Human Anatomy*, first published in 1685.

The court physicians treated Peter for what some believe was syphilis contracted in Amsterdam. Mercurial injections were given in 1706, 1707, and 1708, and various medications were later administered for relief of severe leg pains which might have had a tabetic basis.

Engraved upon Peter's royal seal were the words: "I am of those who seek knowledge and are willing to learn." His immense intellectual curiosity extended even further into medicine. He watched operations and learned to dissect. He even performed minor procedures. A wine merchant's wife who had refused surgery was brought before him and he performed an abdominal paracentesis which yielded 24 pounds of fluid. Unfortunately, the patient died 2 days later and Peter attended her funeral. Especially fond of dentistry, he occasionally extracted a sound tooth. So great was his surgical zeal that he made special instruments which he always carried with him, ready to operate at a moment's notice. His surgical propensities were so well known that the Duchess of Mecklenburg, ill with a boil on her foot, "fled with all the nimbleness in her power from the city in which the august operator was staying" (4). As his boldness and, we hope, his dexterity increased, he undertook major operations but the results are not recorded. He was more upset by erring in surgical technique than he was after decapitating 12,000 soldiers.

Having heard that poorly qualified doctors were occasionally immigrating into Russia, Peter undertook every means to root out the impostors. He personally quizzed suspected quacks and during these examinations displayed much medical knowledge.

In the last 10 years of his life, the lot of his nation improved but his own health worsened. He was tormented by leg pains, coughing spells, insomnia, and hallucinations of ghosts and blood, quite understandable in view of his many murders but also possibly related to central nervous system lues. He constantly needed to urinate and had a definite urethral stricture. By January of 1725 Peter the Great was an invalid and suffered from urinary retention treated with frequent catheterizations by Horne, an English surgeon. On one of these painful occasions Peter allegedly exclaimed, "What a wretched animal is man!" (2). In spite of relief after passing a calculus and

by having a needle cystotomy, he gradually weakened and on 28 January, 1725 he died.

To Peter's other achievements of establishing schools of mathematics and navigation, of importing special breeds of cattle, of building cities, canals, and factories, of editing his country's first newspaper, of revising the coinage system, of simplifying the Russian alphabet and calendar, of codifying table manners and dress must be added his singular contributions to medicine. With justification, this unruly Tsar has been considered a founder of Russian medicine.

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Reviews of New Books

VOLUME I of the publication *Surgery in World War II* has been previously reviewed. Volume II[1] is a continuation of the story of neurologic surgery as practiced in World War II. Again, it is written by a number of men who are authorities on the subjects discussed and by men who had intimate firsthand experience with neurosurgical problems during the course of the last great conflict.

The first volume contained subjects which are of more general interest to a neurologic surgeon than does the present volume under discussion. Volume II is concerned primarily with the care of spinal cord injuries and peripheral nerve injuries. Both of these problems are much more frequent in war time than in civilian life and in World War II were found to be more prevalent than was initially suspected. The discussion on spinal cord injuries is very good and complete. The discussion is not confined alone to the purely neurosurgical aspects of the problem but includes the over-all care of the patients and, in particular, the complications which may occur in other areas, such as bladder care. Wars have always produced interest in the care of peripheral nerve injuries, and World War II certainly offered a superb opportunity for a further study of this problem.

Volume II, as Volume I, is an excellent book for reference use and should be extremely valuable should our country ever find itself again faced with the care of severe neurologic casualties. —*Daniel Ruge.*

REPRESENTED in the book entitled *Photography in Medicine*[2] are the combined efforts of a photographer and a physician writing a volume concerning the aspects of medicine which lend themselves to photography and to indicate the techniques and value of photographic records in medical practice.

As stated in the preface, this book is directed to photographers who have a working knowledge of photography and is intended to supplement textbooks on general photography. The book contains much which would be of value to someone seeking a career in medical photography and also contains many ideas of value to the practicing medical photographer. It also should be of value to the biologist or practicing physician who wishes to make his own photographs.

The book is clearly written and lavishly illustrated. It contains a great deal of information that should be of value to all concerned with the practice of photography in medicine. —*Nicholas Wetzel.*

[1] MEDICAL DEPARTMENT, UNITED STATES ARMY. SURGERY IN WORLD WAR II. Neurosurgery. Vol. II. Prepared and published under the direction of Major General S. B. Hays. Edited by John Boyd Coates, Jr., MC, R. Glen Spurling, M.D., Barnes Woodhall, M.D., and Elizabeth M. McFetridge, M.A. 705 pages, illustrated. $7.00. Washington, D. C.: Office of the Surgeon General, Department of the Army, 1959.

[2] PHOTOGRAPHY IN MEDICINE. By Arthur Smialowski and Donald J. Currie, M.D., M.Sc., F.R.C.S.E., F.R.C.S. (C.), D.S., F.A.C.S. 330 pages, 282 illustrations. $14.50. Springfield, Ill.: Charles C Thomas, 1960.

THE APPEARANCE of the second edition of Buie's *Practical Proctology*[3] is most fortunate and is a welcome addition to proctologic literature. Since the first edition has been out of print, there has been a lack of good texts on proctology.

The second edition of this volume differs from the first in that Buie has drawn generously from the writings and ideas of others. The first edition, for practical purposes, represented the author's personal ideas. The material has been brought up-to-date by including discussions of subjects such as Gardner's syndrome, Peutz-Jegher's disease, newer concepts of cancer spread, the "second-look" operation, and others.

Having the tremendous experience which he gained at the Mayo Clinic and having kept completely abreast of all new ideas and practices, Buie has incorporated into this new book an enormous amount of information, good sense, and practical ideas. The first chapter, "The Responsibility of the Physician," should be read by every medical student and medical practitioner.

For his many friends who regard his ideas as authoritative and for the many physicians, surgeons, and students who will use *Practical Proctology* as a reference work, Buie has performed an outstanding service. —*William C. Bernstein.*

A NEW TEXTBOOK, entitled *Anatomy; a Regional Study of Human Structure*[4] has appeared to compete with traditional texts as a source of information for medical students. Many clinicians are perhaps unaware that, in recent years, there have been several other attempts to produce a textbook of anatomy, shorter and better adapted to a course that has suffered great curtailment in modern curricula. As yet, the older standard texts maintain their dominance, which is partly because they serve both as a student text and as a later source of reference. Admitting that the large books require judiciously selective reading, it can be urged that there is a definite gain from this acquired skill, since much of the student's postgraduate life will have to adapt to a similar regimen. On the other hand, a claim in the interest of immediate efficiency can be made for a concise book which meets for the beginner his early needs and which leaves him with clear concepts of fundamentals.

The present text, written by 3 experienced teachers, is a notable attempt to fill this need. The avowed major aims are: (1) to provide a sufficiently brief text; (2) to supply information on living anatomy, stressing the relationship of structure and function; (3) to introduce abundant references as footnotes and bibliographies in order to show how anatomy is a grow-

[3] PRACTICAL PROCTOLOGY. By Louis A. Buie, Sr., M.D., F.A.C.S. 2nd ed. 737 pages, 280 illustrations. $22.50. Springfield, Ill.: Charles C Thomas, 1960.

[4] ANATOMY; A REGIONAL STUDY OF HUMAN STRUCTURE. By Ernest Gardner, M.D., Donald J. Gray, Ph.D., and Ronan O'Rahilly, M.Sc., M.D. 999 pages, illustrated. $15.00. Philadelphia and London: W. B. Saunders Co., 1960.

ing discipline and where new information can be found. Radiographic anatomy is also sufficiently treated. The plan of presentation is basically regional, to conform to the customary program of dissection, but many general topics of a systematic nature are covered in 10 introductory chapters. Illustrations are line drawings, except for the numerous roentgenograms. Although plentiful and valuable, they do not attempt to supplant the concurrent use of an anatomic atlas. The subdivision of the subject matter into 82 chapters, mostly short, is novel. There is a glossary of eponymous terms and an adequate index.

Unlike the customary treatment in larger texts, histology and neurology have been omitted as such. On the other hand, since comparative anatomic and developmental information is now often acquired by the student before he reaches medical school, some relevant information on these matters is interjected at appropriate places. This new work offers a tantalizing display and distillate of old wine in a new bottle. Moreover, the manner of presentation is refreshingly different and modern. It should be an interesting, and even exciting, book to a new student. It will surely prove a revelation to the practitioner who has never known other than the old time, standard texts.

—Leslie B. Arey.

ALTHOUGH THE BOOK is entitled *Atlas der gynaekologischen Operationen*,[5] this volume is almost as much a textbook of gynecologic surgery. There is an introductory chapter covering preoperative and postoperative treatment. The remainder of the book is divided into 5 sections: (1) minor procedures and operations on the abdominal wall, (2) abdominal operations, (3) vaginal operations, (4) radical and ultraradical carcinoma operations, (5) urologic and proctologic procedures.

The text is well written in simple, lucid language. The 720 illustrations were drawn by K.-H. Seeber and they are beautiful, clear, and instructive. Every gynecologic operation is so thoroughly illustrated that even without a knowledge of the German language, the steps of the operation can be followed easily.

The 5 main sections comprise 20 chapters. At the end of each is a well selected list of references. The authors have covered the literature thoroughly and due credit has been given to all surgeons who have contributed to gynecologic surgery. They also list the 19 foremost books on gynecologic surgery written in English and German.

The book is definitely up-to-date. For example, the authors include descriptions and illustrations on the treatment of cardiac arrest, the incompetent os, both in the nonpregnant and in the gravid state, and feminine pseudohermaphroditism. However, they illustrate the Pomeroy technique of sterilization but not the Irving which they mention and which they state has a lower incidence of failures. The Strassmann operation for double uterus has been illustrated; however, the Jones modification has not been illustrated. The Kocher fixation operation of the uterus for retroflexion, an operation which is rarely done in the United States, is described and illustrated. Two obstetric operations, namely abdominal hysterotomy and cesarean section are included.

The format of the book is excellent. The paper is sturdy and flexible and the extra width of the book makes for easy handling. The binding is also sturdy.

In my opinion this is one of the best atlases of operative gynecology in any language. Both the authors and the publishers are to be congratulated on having produced this outstanding book.

—J. P. Greenhill.

THE IMPORTANCE of treating adolescents as well as their diseases has been successfully emphasized by Roswell Gallagher in his book entitled *Medical Care of the Adolescent*.[6] No inference should be taken that the author is introducing a new specialty, but rather that he seeks to present the adolescent and his problems forthrightly with understanding and sympathy that could well be adopted by any practitioner who deals with patients in this age group.

Comments on the adolescent, his needs, anxieties, strivings, and frustrations are sprinkled with practical aids on history taking that get beneath the apparent complaints and bring the real ones into proper perspective. In similar fashion, hints on physical examination adequately establish criteria for the differences between slow but normal growth and development and abnormal growth states.

Perhaps the major contribution of this writing is a sound yet flexible approach to such subjects as physical fitness, fatigue, participation in athletics, scholastic failure, and obesity. It is refreshing to read of the assessment of these difficulties, their variable etiologies, and plans for management without the usual nebulosity attached to such entities.

Adverse criticism of this book is centered about the latter half in which short chapters are devoted to specific diagnoses, organs and organ systems, and categories of injury or illness. Obviously, exhaustive comment is not possible in a text such as this, and if one seeks herein information more properly to be gleaned from texts in surgery or prediatrics, he will be disappointed. In this text as in no other that I know of, however, the reader will gain much needed insight into a variety of childhood and adult medical problems as they pertain uniquely to adolescents.

—C. Everett Koop.

TWENTY-EIGHT leading British surgeons have contributed to the volume entitled *Recent Advances in Surgery*[7] which is a practical clinical summary of developments in this particular field. The subject matter was carefully selected on the basis of advances in various fields of surgery and those phases which have been clarified from a technical and physiologic standpoint in the recent 5 year period. The sections which will demand the most attention from the reader are those concerning the metastasizing argentaffinoma, the

[5] ATLAS DER GYNAEKOLOGISCHEN OPERATIONEN. By Prof. Dr. O. Käser and Dr. F. A. Iklé. 451 pages, 720 illustrations. $35.25. Stuttgart: Georg Thieme Verlag, 1960.

[6] MEDICAL CARE OF THE ADOLESCENT. By J. Roswell Gallagher M.D. 369 pages, 43 illustrations. $10.00. New York: Appleton-Century-Crofts, Inc., 1960.

[7] RECENT ADVANCES IN SURGERY. Edited by Selwyn Taylor, D.M., M.Ch., F.R.C.S. Foreword by Sir James Paterson Ross, K.C.V.O., M.S. 5th ed. 500 pages, 160 illustrations. $13.00. Boston: Little, Brown & Co., 1959.

place of ablative surgery including hypophysectomy and adrenalectomy for malignancy, the undescended testicle, and cardiac surgery. These, however, are but a few of the chapters, and the volume does include such subjects as surgery for portal hypertension, liver resection, partial nephrectomy, ischemia of the leg, gastrointestinal tumors, and inflammatory conditions at surgery.

Essentially, the importance of this book is to condense in readable and understandable form the volume of medical literature which has been written about these numerous subjects. It thus serves as a critical review in summarizing the general experience of surgeons from various areas of the world, and its value is enhanced by the excellent choice of contributors who have collected not only the best of the general information but who have also added valuable material from their own experience. Increasing emphasis has also been placed upon the importance of biochemistry and physiology in the disease processes and in the management of various disease states for which surgical excision was at one time considered most important. This trend is covered satisfactorily in the references to the argentaffinoma and to serotonin, the use and contraindications for the artificial kidney, and the subject of ammonia metabolism.

—*W. Harrison Mehn.*

THE EXCELLENT BOOK *The Placenta and Fetal Membranes*[8] has been planned so as to be of value to both the student and the experienced investigator. Part 1, which consists of 8 reviews of placental anatomy, biochemistry, function, and pathology written by experts in each field, should be required reading for medical students, particularly those who plan to follow any phase of reproduction. Aside from the usual presentation of textbooks, each of these reviews delves deeply into its respective subject and presents data and ideas which are completely current.

For those who wish to become more familiar with the material and the smaller details, Part II is a transcript of the November 1958 proceedings of the conference at Princeton, New Jersey, which was devoted to a complete discussion of current research on the placenta. Although, at times, it is a bit confusing to follow, for the most part the content is nonetheless invaluable.

Parts III and IV are devoted to a survey of the literature and a list of current investigations, respectively. This complete bibliography would certainly simplify the task of reviewing the problems of the placenta or placentation. The list of current research with its principal and associated investigators provides an up-to-date listing of those who are active in this field. Also, for anyone embarking upon research in this field, it is an excellent reference to the work which has been done, as well as to areas in which further work might be productive.

In summary, this book provides an excellent source of facts and figures about the placenta and its function, and it also serves as a starting point for further research.

—*J. W. Roddick, Jr.*

[8]THE PLACENTA AND FETAL MEMBRANES. Edited by Claude A. Villee. 404 pages, illustrated. $10.00. Baltimore: The Williams & Wilkins Co., 1960.

THE BOOK entitled *Cancer and Allied Diseases of Infancy and Childhood*[9] is in many ways an extension of a similar book on this disease in adults. It contains generally a considerable amount of useful information.

In the introduction there is an excellent discussion of the general characteristics of tumors in infants and children and a comparison of the differences between these tumors and those encountered in adults.

As is often the case in textbooks of multiple authorship, the quality of the material presented varies considerably from one section to another. The sections on the chest, the nervous system, and lesions of the neck are particularly well written. The section by Debier is especially commendable since both common and rare lesions of the neck encountered in children are presented in a well organized manner. These portions of the book are good sources of reference. There are other sections which are not as well planned, such as those dealing with Wilms's tumor and neuroblastoma. One has the impression that these sections are from contributors who are primarily interested in those tumors found in adults and who have not devoted a great deal of attention to the special problems involved with childhood. It is unfortunate that some centers which have the greatest experience with these common tumors in children are not represented among the contributors. Obviously, several sections are written with the purpose of aiding diagnosis rather than therapy. When therapy is included, the details of the surgical procedures involved are not given. One has the feeling that the Editors do not wish to emphasize this aspect of the entire problem. Considerable space is devoted to descriptions of unusual cases. Although this is interesting reading, it is of little value to the physician who is seeking help in the problem of diagnosis of a tumor. However, as a reference book, it is quite satisfactory and, undoubtedly, will be useful to pediatricians and physicians.

—*Orvar Swenson.*

THE WORTHWHILE MONOGRAPH entitled *Cardiac Resuscitation*[10] is a result of a symposium sponsored by the Department of Medicine of Emory University School of Medicine on 3 October 1958. It is especially significant in that the Editor is a Professor of Medicine, and the contributors include a neurologist, cardiologist, 2 anesthesiologists, a surgeon, lawyer, and theologian. Hurst has viewed the problems of cardiac resuscitation from many vantage points. As a participant in the panel, Zoll's remarks have been thoughtfully presented from the viewpoint of the internist. He has summarized much of the present status of the use of the external electric cardiac pacemaker and external electric defibrillator. A good deal of factual information is provided in this regard. The panel does not attempt to present controversial viewpoints nor is much effort spent in documenting the opinions expressed. This approach, however, does not detract from the effectiveness of this book. The monograph lends itself to rather

[9]CANCER AND ALLIED DISEASES OF INFANCY AND CHILDHOOD. Edited by Irving M. Ariel, M.D., and George T. Pack, M.D. 27 contributing authors. 605 pages, illustrated. $22.50. Boston and Toronto: Little, Brown & Co., 1960.

[10]CARDIAC RESUSCITATION. Edited by J. Willis Hurst, M.D. 141 pages, illustrated. $5.50. Springfield, Ill.: Charles C Thomas, 1960.

rapid reading, and it has been illustrated when necessary. Some overlap of material by the panelists is not unexpected. Most physicians would profit by a review of the chapter on respiratory resuscitation and might well view the teaching movie described by the author of this chapter. Editing mistakes have been minimal except for some misspelling of names in the bibliography. A very interesting discussion of the etiologic and therapeutic approach to cerebral anoxia is presented.

The internist will find answers to many of his questions about the indications for cardiac resuscitation.

—*Hugh E. Stephenson, Jr.*

NEUROSURGICAL PROCEDURES rather than the indications for them are dealt with in the volume entitled *An Atlas of Neurosurgical Techniques*.[11] The stages of neurosurgical operations have been presented by the author from start to finish so that they may be performed in as orderly a fashion as possible. In this, he has been successful. The field of operative neurosurgery is covered thoroughly and the clear, well chosen illustrations are neither too few nor too numerous. The accompanying text is concise and pertinent. Many details of technique which have proved valuable to the author are included. It is unfortunate that the understandably high price of this book may place it beyond the reach of the neurosurgical resident and younger neurosurgeon to whom it would be most valuable.

—*Stanford Larsen.*

THE MALE GERMINAL GLAND is the subject of the monograph entitled *Die Maennliche Keimdruese*[12] which deals with the endocrine and spermatogenic functions of the testis. This book is the result of a 9 year collaboration of 4 outstanding authorities on a study of hypogonadism in the male. The anatomic, physiologic, biochemical, and clinical aspects of normal and abnormal testicular function are presented in detail. Although the material contained in this volume is of a highly technical and specialized nature, it is presented in such a clear, simple manner that it can be readily understood even by those readers who do not happen to be experts in this field.

The authors have succeeded in bringing order to what is frequently a confusing and bewildering subject. The 176 pages of text contain 38 illustrations and 16 tables. At the end of the volume is an atlas of 31 pages containing 78 magnificent illustrations. The photomicrographs of the testicle are superb and show evidence of outstanding histologic and photographic techniques. The field of testicular histology is perplexing even to a trained general pathologist. In these photomicrographs, however, even the uninitiated will readily learn to recognize Leydig cells, Sertoli cells, and the various stages of spermatogenesis. This section alone would make the book worth while.

—*Frederick A. Lloyd.*

IN HIS NEW BOOK, *Surgical Gastroenterology*,[13] Bowers has presented the entire subject concisely for reference by the general practitioner. Except for the chapter on "Diagnostic Methods," the book was written by the author, and it bears his definite personal imprint.

Every gastrointestinal surgeon will challenge certain statements that have been made because the author has presented his own views about the theory and management of all gastroenterologic diseases. However, he does refer fairly and adequately to the significant contributions in each field, agreeing or disagreeing with the views expressed in the light of his own considerable experience. Each subject is clearly presented, and the author has done a fine job in reserving longer discussions for the common and problem diseases, and discussing the rarities with a few sentences. Occasionally, the author chides a number of present day young surgeons who cannot give surgical care without a radiation badge, slide rule, and all the niceties of a high-powered research hospital; he gives the impression that his personal surgical credo embraces a more direct and less complicated approach with avoidance of frills. An occasional castigation of his surgical confreres and, in fact, a number of vitriolic comments about a special breed of surgeons add spice to the text and make the reading more entertaining.

The book is artistically bound and printed; it is well illustrated, and, consequently, is easy and pleasant to read. Following each chapter is a good bibliography; however, several of these are too long.

This work is not complete enough for gastroenterologists, medical or surgical, but it meets adequately the author's goal; it is an excellent reference for the family doctor.

—*Irving F. Enquist.*

ONE COULD conveniently divide the 373 page book entitled *Outline of Orthopaedics*[14] into 3 separate sections. The first section, 30 pages in length, deals with the clinical methods applicable to orthopedic surgery and is largely devoted to history, physical examination, and the principles of treatment. The second section, 100 pages, consists of a general survey of orthopedic disorders given in an expanded outline form. The author arbitrarily uses a 5 division outline consisting of deformities, affections of joints, affections of bone, affections of soft tissues, and neurologic disorders. Fractures are not included except when the complications are of significance within this outline form. The third section covers essentially the same material but it has been reclassified according to anatomic location. This matter also has been given in an expanded outline form, and each new anatomic area considered has a preliminary outline of the method of examination of this area. This latter addition seems somewhat superfluous since the principles involved are covered in the first section.

This book is exactly what its title indicates, an out-

[11] AN ATLAS OF NEUROSURGICAL TECHNIQUES. By James L. Poppen, M.D. 522 pages, 248 illustrations. $28.00. Philadelphia and London: W. B. Saunders Co., 1960.

[12] DIE MAENNLICHE KEIMDRUESE. STRUKTURE, FUNKTION, KLINIK. GRUNDZUEGE DER ANDROLOGIE. By Prof. Dr. E. Tonutti, Priv.-Doz. Dr. O. Weller, Prof. Dr. E. Schuchardt, and Prof. Dr. E. Heinke. 268 pages, illustrated. DM 79— Stuttgart: Georg Thieme, 1960.

[13] SURGICAL GASTROENTEROLOGY; CONSIDERATIONS BASED ON PATHOLOGIC PHYSIOLOGY. By Warner F. Bowers, A. B., B.Sc., M.D., M.Sc., Ph.D. (Surg.). 498 pages, 235 illustrations. $18.50. Springfield, Ill.: Charles C Thomas, 1960.

[14] OUTLINE OF ORTHOPAEDICS. By John Crawford Adams, M.D. (Lond.), F.R.C.S. (Eng.). 3rd ed. 440 pages, 313 illustrations. $8.00. Edinburgh and London: E. & S. Livingstone Ltd., 1960; Baltimore: The Williams & Wilkins Co., exclusive U. S. agents.

line of orthopedics. The author states that it is primarily intended for students studying for qualifying examinations, for physiotherapists, and orthopedic nurses. This is the third edition since 1955, and it would appear to fulfill its purpose.

—*Edwin G. Bovill, Jr.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

ELECTROENCEPHALOGRAPHY IN ANESTHESIOLOGY. By Albert Faulconer, Jr., M.D., M.S., and Reginald G. Bickford, M.B., Ch.B., M.R.C.P. 90 pages, 35 illustrations. $4.75. Springfield, Ill.: Charles C Thomas, 1960.

LA COLITE ULCEROSA. By Antonello Franchini and Leonardo Possati. Preface by G. Placitelli. 250 pages, 73 illustrations. Bologna: Capitol Editrice, 1960.

OUR OBSTETRIC HERITAGE; THE STORY OF SAFE CHILDBIRTH. By Herbert Thoms, M.D. 164 pages, illustrated. $4.75. Hamden, Conn.: The Shoe String Press, 1960.

L'INFECTION STAPHYLOCOCCIQUE. By Robert Worms. 442 pages. Paris: Editions Medicales Flammarion, 1960.

DISEASES OF THE NEWBORN. By Alexander J. Schaffer, M.D. With a section on neonatal cardiology by Milton Markowitz, M.D. 878 pages, 341 illustrations. $20.00. Philadelphia and London: W. B. Saunders Co., 1960.

MEDICAL PHYSIOLOGY AND BIOPHYSICS. 18th ed. of Howell's Textbook of Physiology. Edited by Theodore C. Ruch, Ph.D., and John F. Fulton, M.D. 1232 pages, 616 illustrations. $16.00. Philadelphia and London: W. B. Saunders Co., 1960.

FIRST CANADIAN SYMPOSIUM ON NON-GONOCOCCAL URETHRITIS AND HUMAN TRICHOMONIASIS; MONTREAL 1959. Edited by Zoltan Gallai and Lucien Sylvestre. 434 pages, illustrated. $15.40. Basel: S. Karger AG., 1960. White Plains, N. Y.: Albert J. Phiebig, American Representative.

THE TONSILS AND ADENOIDS IN CHILDHOOD. By Donald F. Proctor, M.D. 70 pages, 23 illustrations. $7.50. Springfield, Ill.: Charles C Thomas, 1960.

ST. PETER'S HOSPITAL FOR STONE. Edited by Clifford Morson, O.B.E., F.R.C.S. 64 pages, illustrated. $5.00. Edinburgh and London: E. & S. Livingston Ltd., 1960; Baltimore: The Williams & Wilkins Co., exclusive U. S. agents.

KLINISCHE CHIRURGIE FUER DIE PRAXIS. By Prof. O. Diebold, Prof. H. Junghanns, and Prof. L. Zukschwerdt. Vol. III. 148 pages, illustrated. $6.70. Stuttgart: Georg Thieme, 1960.

SURGICAL ERRORS AND SAFEGUARDS. 5th ed. By Max Thorek, M.D., LL.D., Sc.D., F.I.C.S., F.B.C.S., F.P.C.S.(Hon.), D.C.M., F.R.S.M. 652 pages, 455 illustrations. $25.00. Philadelphia and Montreal: J. B. Lippincott Co., 1960.

PRACTICAL CLINICAL MANAGEMENT OF ELECTROLYTE DISORDERS. By William J. Grace, M.D. 132 pages. $4.95. New York: Appleton-Century-Crofts, Inc., 1960.

HEMORRAGIAS GRAVES DEL TRACTO DIGESTIVO SUPERIOR (ESOFAGO, ESTOMAGO, DUODENO, HIGADO, PANCREAS, YEYUNO). By Pedro Larghero in collaboration with Eugenio R. Zerboni and Marcos Santa-Rosa. 131 pages, 206 illustrations. Montevideo: Hospital Pasteur, 1960.

HEMATOMAS INTRACRANEANOS TRAUMATICOS. By Pedro Larghero Ybarz. 312 pages, illustrated. Buenos Aires: Inter-medica Editorial, 1959.

INTRASPINAL TUMORS OF CHILDHOOD. By Robert W. Rand, M.D., Ph.D., and Carl W. Rand, M.D. 560 pages, 245 illustrations. $16.50. Springfield, Ill.: Charles C Thomas, 1960.

EXPERIENCES WITH CONGENITAL BILIARY ATRESIA. By Julian A. Sterling, M.D., Sc.D., F.A.C.S. 68 pages, 19 illustrations. $5.50. Springfield, Ill.: Charles C Thomas, 1960.

FRACTURES, DISLOCATIONS, AND SPRAINS. By Philip Wiles, M.S.(Lond.), F.R.C.S. (Eng.), F.A.C.S. 67 pages, 519 illustrations. $7.50. Boston: Little, Brown & Co., 1960.

A TEXTBOOK OF SURGICAL PATHOLOGY. 8th ed. By C. F. W. Illingworth, C.B.E., M.D., Ch.M., F.R.C.S.(Ed.), F.R.F.P.S.(Glas.), Hon. F.A.C.S., Hon. F.R.C.S.(Eng.), and Bruce M. Dick, M.B., F.R.C.S.(Ed.), F.R.F.P.S.(Glas.). 700 pages, 329 illustrations. Boston: Little, Brown & Co., 1960.

GYNECOLOGICAL UROLOGY. Compiled and edited by Abdel Fattah Youssef, M.B., D.S., D.G.O., M.Ch., F.I.C.S. With a foreword by Naguib Mahfouz, M.Ch., F.R.C.S.(Hon.), F.R.C.P., F.R.C.O.G.(Hon.). 890 pages, illustrated. $22.50. Springfield, Ill.: Charles C Thomas, 1960.

SELECTED PAPERS. By Sir Geoffrey Jefferson. 562 pages, illustrated. $22.00. Springfield, Ill.: Charles C Thomas, 1960.

HERNIAS DIAFRAGMATICAS DEL HIATO ESOFAGICO. By Dr. Manuel A. Casal. 158 pages, 94 illustrations. Buenos Aires: Lopez & Etchegoyen, 1959.

DEMONSTRATIONS OF PHYSICAL SIGNS IN CLINICAL SURGERY. 13th ed. By Hamilton Bailey, F.R.C.S. (Eng.) F.A.C.S., F.R.S.E. 927 pages, 1142 illustrations. $14.50. Baltimore: The Williams & Wilkins Co., 1960.

Correspondence

ARTERIAL EMBOLISM IN THE LIMBS by A. L. Jacobs—*A Correction.*

DR. WYLIE has indicated that the last 2 sentences in the next to the last paragraph of his review of this book which appeared in the August 1960 issue of the Journal on page 252 should have read: "The author limits advice for embolectomy to saddle emboli and to all cases of embolism of the iliac, femoral, or axillary arteries in which signs of grave ischemia are still present 2 or more hours after the onset of symptoms. In this era of reconstructive surgery for disabling arterial occlusion, acute or chronic, many American surgeons would object to withholding the relatively simple operation of embolectomy."